GILEAD Galápagos

CLINICAL STUDY PROTOCOL

Study Title:	A Phase 3, Randomized, Double-blind, Placebo and Adalimumab-controlled Study to Evaluate the Efficacy and Safety of Filgotinib in Subjects with Active Psoriatic Arthritis Who Are Naïve to Biologic DMARD Therapy	
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA	
IND Number:	115510	
EudraCT Number:	2019-001996-35	
Clinical Trials.gov Identifier:	NCT04115748	
Indication:	Psoriatic Arthritis	
Protocol ID:	GS-US-431-4566	
Gilead Clinical Operations:	Name: Telephone:	PPD PPD
PPD	Name: Telephone: Fax:	PPD PPD PPD
Protocol Version/Date:	Original: Amendment 1: VHP Amendment 1.1: Amendment 2:	16 May 2019 07 August 2019 11 December 2019 17 April 2020

This study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312); however, sites located in the European Economic Area and Switzerland are not included under the IND and are considered non-IND sites.

CONFIDENTIALITY STATEMENT

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

PROTOCOL SYNOPSIS

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Study Title:	A Phase 3, Randomized, Double-blind, Placebo and Adalimumab-controlled Study to Evaluate the Efficacy and Safety of Filgotinib in Subjects with Active Psoriatic Arthritis Who Are Naïve to Biologic DMARD Therapy
IND Number:	115510
EudraCT Number:	2019-001996-35
Clinical Trials.gov Identifier:	NCT04115748
Study Sites Planned:	Approximately 430 sites
Objectives:	**The primary objective of this study is:** • To evaluate the effect of filgotinib compared to placebo in active psoriatic arthritis (PsA) as assessed by the American College of Rheumatology 20% improvement (ACR20) response at Week 12 **Secondary objectives of this study are:** • To evaluate the effect of filgotinib on core domains of PsA as assessed by Minimal Disease Activity (MDA) and Very Low Disease Activity (VLDA), ACR responses, Psoriasis Area and Severity Index including Body Surface Area (PASI including BSA) responses, Spondyloarthritis Research Consortium of Canada Enthesitis Index and Leeds Enthesitis Index (SPARCC Enthesitis Index and LEI), Leeds Dactylitis Index (LDI), Psoriatic Arthritis Disease Activity Score (PASDAS), Disease Activity Index for Psoriatic Arthritis (DAPSA), Modified Nail Psoriasis Severity Index (mNAPSI), and Physician's Global Assessment of Psoriasis (PhGAP) • To evaluate the effect of filgotinib on physical function in active PsA as assessed by Health Assessment Questionnaire – Disability Index (HAQ-DI)

	• To evaluate the effect of filgotinib on fatigue and quality of life in active PsA as assessed by Functional Assessment of Chronic Illness Therapy – Fatigue Scale (FACIT-Fatigue), 36-item Short-Form Health Survey Version 2 (SF-36v2), and 12-item Psoriatic Arthritis Impact of Disease (PsAID-12) • To evaluate the efficacy of filgotinib versus adalimumab in active PsA as assessed by ACR20 response • To evaluate the safety and tolerability of filgotinib • See Section 2 for full list of study objectives
Study Design:	This is a randomized, double-blind, placebo- and active-controlled, Phase 3 study in adult male and female subjects with active PsA who have had an inadequate response or intolerance to 1 or more therapies for PsA, such as conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), apremilast and / or non-steroidal anti-inflammatory drugs (NSAIDs), but have never received a biologic DMARD (bioDMARD) for PsA or psoriasis. The study consists of two parts, the Main Study: Screening through Week 16 (inclusive) and the Long Term Extension (LTE): after Week 16 for 2 years. After all subjects have completed the Week 16 Visit or have permanently discontinued the study prior to Week 16, the treatment assignments will be unblinded to the Sponsor only. The subjects and investigators will remain blinded to individual level treatment assignment. **Part 1 – Main Study (Screening through Week 16):** Approximately 854 subjects will be randomized in a 2:2:1:2 ratio to one of 4 dosing groups as outlined below. Randomization will be stratified by geographic region and concurrent use of csDMARD(s) and / or apremilast at randomization (yes or no). Subjects will be permitted, but are not required, to continue stable doses of background csDMARD(s), apremilast, and / or NSAIDs. Every effort should be made to maintain stable background therapy for PsA treatment through the completion of the Week 16 Visit. Instructions for rescue therapy are detailed in Section 5.4.

Dosing groups in the Main Study:

- Filgotinib 200 mg group: **filgotinib 200 mg once daily** + placebo to match (PTM) filgotinib 100 mg once daily + PTM adalimumab subcutaneous (SC) injection once every two weeks (q2w)
- Filgotinib 100 mg group: PTM filgotinib 200 mg once daily + **filgotinib 100 mg once daily** + PTM adalimumab SC injection q2w
- Active comparator group: PTM filgotinib 200 mg once daily + PTM filgotinib 100 mg once daily + **adalimumab 40 mg SC injection q2w**
- Placebo control group: PTM filgotinib 200 mg once daily + PTM filgotinib 100 mg once daily + PTM adalimumab SC injection q2w

NOTE: All subjects will discontinue adalimumab / PTM injections by the Week 16 Visit (the last injections should be at approximately Week 14).

Part 2 – LTE (After the Week 16 Visit for 2 years):

After completion of the Main Study, subjects who have not permanently discontinued study drug will continue on to the LTE as follows:

- Those who were assigned to the filgotinib groups will continue on the same study drug assignments
- Those who were assigned to the placebo or active comparator groups will be reassigned 1:1 in a blinded fashion to filgotinib 200 mg or 100 mg once daily

Dosing groups in the LTE:

- Filgotinib 200 mg group: **filgotinib 200 mg once daily** + PTM filgotinib 100 mg once daily
- Filgotinib 100 mg group: PTM filgotinib 200 mg once daily + **filgotinib 100 mg once daily**

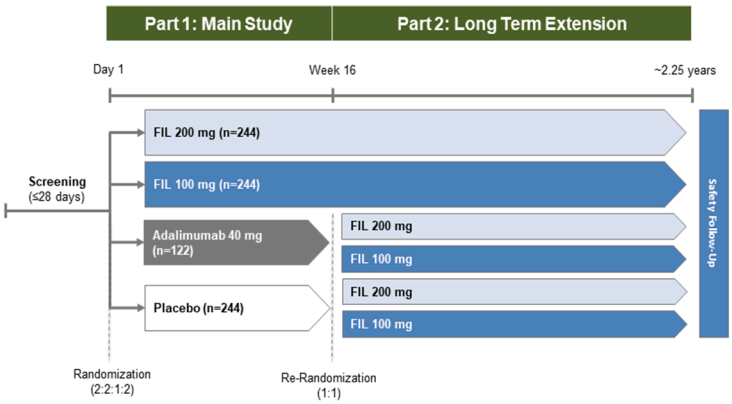
Discontinuation of Study Drug:

For the first 16 weeks of study participation, subjects who temporarily interrupt or permanently discontinue study drug for any reason are to continue with study visits and assessments through the Week 16 Visit, per Section 3.5 unless the subject withdraws consent, is lost to follow-up, and / or continued participation in the study is medically contraindicated, per investigator's judgment. Study drug interruption and discontinuation considerations are outlined in Section 3.5. All subjects who permanently discontinue study drug should continue to receive standard of care treatment for their PsA including additional therapies, if required.

Discontinuation of Study Participation:

If a subject is unable to complete the study through the Week 16 Visit, and has received at least one dose of study drug, the subject will complete an Early Termination (ET) Visit at the time of study discontinuation. Subjects will also complete a post-study follow-up visit approximately 4 weeks later (Safety Follow-up Visit).

After the Week 16 Visit, subjects who permanently discontinue study drug for any reason are to discontinue the study. Subjects who exit the study early, regardless of dosing duration, are to complete an ET Visit and a Safety Follow-up Visit.



Number of Subjects Planned:	Approximately 854
Target Population:	Subjects with active PsA despite non-bioDMARD therapies: csDMARD(s), apremilast and / or NSAID(s)
Duration of Treatment:	Approximately 2.25 years
Diagnosis and Main Eligibility Criteria:	For a complete list of study inclusion and exclusion criteria, please refer to Section 4.2 and 4.3. **Key Eligibility Criteria** Key Inclusion Criteria: • Male or female subjects who are 18-75 years of age (19-75 years of age at sites in Republic of Korea, 20-75 years of age at sites in Japan and Taiwan) on the day of signing initial informed consent • Meet Classification Criteria for Psoriatic Arthritis (CASPAR) and have a history consistent with PsA ≥6 months at Screening

- Have active PsA defined as ≥3 swollen joints (from a 66 swollen joint count [SJC]) and ≥3 tender joints (from a 68 tender joint count [TJC]) at Screening and Day 1; these may or may not be the same joints at Screening and Day 1
- Must have a documented history or active signs of at least one of the following at Screening:
  a) Plaque psoriasis
  b) Nail changes attributed to psoriasis
- Have had inadequate response or intolerance to ≥1 csDMARD, apremilast and / or NSAID, administered over the course of ≥12 weeks for the treatment of PsA, as per local guidelines / standard of care
- If continuing csDMARD(s) during the study, subjects are permitted to **use only a maximum of 2 of the drugs as outlined in Section 4.2** and must have been on this treatment for ≥12 consecutive weeks prior to Screening, with a stable dose and route of administration (defined as no change in prescription) for ≥4 weeks prior to Day 1
- Concomitant NSAIDs or corticosteroids are permitted as specified in Sections 4.2 and 4.3.

Key Exclusion Criteria

- Prior PsA or psoriasis treatment with a bioDMARD
- Prior exposure to a JAK inhibitor >2 doses
- Any active / recent infection, as specified in Section 4.3
- Any chronic and / or uncontrolled medical condition that would put the subject at increased risk during study participation or circumstances which may make a subject unlikely or unable to complete or comply with study procedures and requirements, per investigator judgement
- Any moderately to severely active musculoskeletal or skin disorder other than PsA or plaque psoriasis that would interfere with assessment of study parameters, as per judgement of investigator

NOTE: Prior history of reactive arthritis or axial spondyloarthritis is permitted if there is documentation of change in diagnosis to PsA or additional diagnosis of PsA

- Any history of an inflammatory arthropathy with onset before age 16 years old
- Active autoimmune disease that would interfere with assessment of study parameters or increase risk to the subject by participating in the study (e.g. uveitis, inflammatory bowel disease, uncontrolled thyroiditis, systemic vasculitis, transverse myelitis), per judgement of investigator
- Presence of any extra-articular manifestations typically associated with rheumatoid arthritis (RA), such as rheumatoid nodules, rheumatoid lung, or other signs / symptoms, as per judgement of investigator
- Pregnancy or nursing females
- Active drug or alcohol abuse, as per judgement of investigator
- Unwilling or unable to follow protocol requirements

Magnetic Resonance Imaging (MRI) Investigation Key Eligibility Criteria

Key MRI Inclusion Criteria:

- Subject must fulfill criteria for entry to the Main Study
- Subject must have PsA joint involvement at a minimum in one hand / wrist as confirmed by the investigator at Screening. The same hand / wrist (R or L) should be imaged at all subsequent MRIs, regardless of PsA activity.
- Subject's baseline MRI must fulfill at least one of the below criteria by central reading:

  a) Definitive intra-articular MRI synovitis

  OR

  b) Definitive MRI osteitis

Key MRI Exclusion Criteria

NOTE: Subject may still participate in the Main Study / LTE if ineligible for the MRI investigation. Reasons for ineligibility may include, but are not limited to:

- Inability or medical contraindication for an MRI examination (e.g. presence of a pacemaker, defibrillator, or other contraindicated implanted metallic device, such as anterior interbody cages, aneurysm clip or pedicle screws, severe claustrophobia or weight >350 lbs./158 kg)
- Metallic fragments embedded anywhere in the body OR pigment-containing tattoos in the area of examination

	• Known or potential risk of adverse reaction to gadolinium-based contrast agents, including but not limited to, allergy or compromised renal function, per investigator judgement • Very difficult peripheral intravascular access • Site or region was not selected by Sponsor to perform MRIs
Study Procedures/ Frequency:	Refer to Study Procedures Table Appendix 2.
CCI [redacted]	[redacted]
Test Product, Dose, and Mode of Administration:	200 mg filgotinib orally once daily 100 mg filgotinib orally once daily
Reference Therapy, Dose, and Mode of Administration:	Adalimumab 40 mg SC injection (active comparator) or PTM SC q2w PTM filgotinib 200 mg orally once daily PTM filgotinib 100 mg orally once daily
Criteria for Evaluation:	
Safety:	Safety will be assessed by the documentation of AEs, physical examinations, vital signs, and clinical laboratory parameters at specified time points during the study.
Efficacy:	The primary endpoint is the ACR20 response at Week 12. The key secondary endpoints include: • ACR50 response at Week 12 • Change from Baseline in HAQ-DI at Week 12 • Change from Baseline in SF-36v2 physical component summary (PCS) at Week 16 • Change from Baseline in LEI at Week 16, in subjects with enthesitis at Baseline • Psoriasis Area and Severity Index 75% improvement (PASI75) response at Week 16, in subjects with psoriasis covering ≥3% of the BSA at Baseline

- MDA response at Week 16
- Change from Baseline in FACIT-Fatigue at Week 16
- Change from Baseline in LDI at Week 16, in subjects with dactylitis at Baseline

CCI [redacted]

Statistical Methods:

The primary analysis set for efficacy analyses will be the Full Analysis Set, which includes all randomized subjects who received at least one dose of study drug. The primary analysis set for safety analyses will be the Safety Analysis Set, which includes all subjects who received at least one dose of study drug.

All continuous efficacy endpoints will be summarized using an 8-number summary (n, mean, standard deviation [SD], median, 1st quartile [Q1], 3rd quartile [Q3], minimum, maximum) by treatment group. All categorical efficacy endpoints will be summarized with the number and percentage of subjects who meet the endpoint or category definition by treatment group.

Safety endpoints will be summarized with the number and percentage of subjects with events or abnormalities for categorical values or 8-number summary (n, mean, SD, median, Q1, Q3, minimum, maximum) for continuous data by treatment group.

A pre-specified Week 16 analysis is planned after all randomized subjects have completed their Week 16 Visit (or prematurely discontinued from the study prior to Week 16). The time point of the primary efficacy endpoint is Week 12. The time points of the key secondary efficacy endpoints are either Week 12 or Week 16.

The primary efficacy estimand corresponds to the treatment policy strategy. A logistic regression analysis with treatment groups and stratification factors in the model will be used to analyze the primary endpoint.

The graphical approach to sequentially rejective multiple test procedures (Appendix 6 and Appendix 7) will be used to control a family-wise type I error rate at 5% (i.e. $\alpha = 0.05$). Within each filgotinib dosing regimen, the primary hypothesis will be first tested at $\alpha/2$. If the primary hypothesis is rejected, then the next secondary hypothesis in the same filgotinib dosing regimen will be tested at $\alpha/2$. Testing of the hypotheses happens sequentially in the same filgotinib dosing regimen. Once all hypotheses within the same filgotinib dosing regimen are rejected, then the respective $\alpha/2$ can be passed on to the other regimen's hypotheses, that is, all hypotheses in the other filgotinib dosing regimen will be tested at α level.

Two safety estimands, treatment policy and while on treatment, will be applied for the safety analysis.

Sample size is determined based on the non-inferiority test of each filgotinib group compared to the adalimumab group on the ACR20 response rate at Week 12. When assuming the ACR20 response rate being 52% and 60% for the adalimumab and each filgotinib group, and 38.6% for the placebo group, 244 subjects in each filgotinib group and placebo group, and 122 subjects in the adalimumab group are required to obtain 90% power at a two-sided 0.025 significance level to demonstrate that filgotinib group preserves more than 50% of the effect of adalimumab with respect to the ACR20 response rate at Week 12.

A sample size of 244 subjects in each filgotinib group and the placebo group will provide over 95% power to detect a difference in ACR20 response rate of 21.4% at Week 12 (38.6% and 60% for the placebo group and each filgotinib group, respectively) using a two-sided 0.025 significance level superiority test.

In summary, the total sample size will be approximately 854 subjects.

This study will be conducted in accordance with the guidelines of Good Clinical Practice (GCP) including archiving of essential documents.

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

Ab	antibody
ACR	American College of Rheumatology
ADA	adalimumab
ADL	Activities of Daily Living
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
ALT	alanine aminotransferase
anti-TNF	anti-tumor necrosis factor
ApoA1 / B	Apolipoprotein A1 / B
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the curve
CCI	[redacted]
bioDMARD	biologic DMARD
BSA	body surface area
CASPAR	Classification Criteria for Psoriatic Arthritis
CD	Crohn's disease
CES	carboxylesterases
CIA	collagen-induced arthritis
CK	creatine kinase
CNS	central nervous system
eCRF	electronic case report form
CRO	contract research organization
CRP	C-reactive protein
csDMARDs	conventional synthetic disease-modifying anti-rheumatic drugs
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CVEAC	Cardiovascular Event Adjudication Committee
CYP	cytochrome P450
DAPSA	Disease Activity in Psoriatic Arthritis
DAS28	Disease Activity Score 28
DBP	diastolic blood pressure
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
DSS	dextran sulphate sodium
ECG	electrocardiogram
EDC	Electronic Data Capture
EQ-5D-5L	EuroQol 5 Dimensions with 5 Levels

eSAE	Electronic Serious Adverse Event
ET	Early Termination
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy – Fatigue Scale
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
GSI	Gilead Sciences, Inc.
h	hours
HAQ-DI	Health Assessment Questionnaire - Disability Index
HbA1c	Hemoglobin A1c
HBsAg	HBV surface antigen
HBV	hepatitis B virus
HCRU	Healthcare Resource Utilization Questionnaire
HCV	hepatitis C virus
HDL	high-density lipoprotein
HDPE	high density polyethylene
hERG	human ether-a-gogo related gene
HIV	human immunodeficiency virus
HLA-B27	Human Leukocyte Antigen B27
HLGT	High-Level Group Term
HLT	High-Level Term
HR	heart rate
IB	investigator's brochure
IBD	inflammatory bowel disease
IC50	inhibitory concentration
ICF	Informed consent form
ICH	International Conference on Harmonization
IL	interleukin
IRB / IEC	Institutional Review Board or Independent Ethics Committee
IXRS	Interactive Voice / Web Response System
JAK	janus kinase
LDA	low disease activity
LDI	Leeds Dactylitis Index
LDL	low-density lipoprotein
LEF	leflunomide
LLT	Lower-Level Term
LTE	Long Term Extension
MACEs	major adverse cardiovascular events
MCS	Mental Component Score

MDA	Minimal Disease Activity
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effect model repeated measures
mNAPSI	Modified Nail Psoriasis Severity Index
MSS	Medical Safety Science
MRI	Magnetic Resonance Imaging
MTX	methotrexate
NOELs	no-observed-effect-levels
NSAIDs	non-steroidal anti-inflammatory drugs
NYHA	New York Heart Association
OATs	organic anion transporters
PASDAS	Psoriatic Arthritis Disease Activity Score
PASI including BSA	Psoriasis Area and Severity Index including Body Surface Area
PASI75	Psoriasis Area and Severity Index 75% improvement
PCS	physical component summary
PD	pharmacodynamics
PDE4	phosphodiesterase 4
PEG	polyethylene glycol
PGADA	Patient's Global Assessment of Disease Activity
PGAPI	Patient's Global Assessment of PsA Pain Intensity
P-gp	P-glycoprotein
PhGADA	Physician's Global Assessment of Disease Activity
PhGAP	Physician's Global Assessment of Psoriasis
PK	Pharmacokinetic
PROs	Patient Reported Outcomes
PsA	psoriatic arthritis
PsAID-12	12-item Psoriatic Arthritis Impact of Disease
PsAMRIS	Psoriatic Arthritis Magnetic Resonance Imaging Score
PsARC	Psoriatic Arthritis Response Criteria
PT	Preferred Term
PTM	placebo to match
PVE	Pharmacovigilance and Epidemiology
Q1	1st quartile
q2w	Once every two weeks
Q3	3rd quartile
qd	Once daily
QFT	QuantiFERON® TB Gold Plus
RA	rheumatoid arthritis
SADRs	serious adverse drug reactions
SAE	Serious adverse events

SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SC	subcutaneous
SD	standard deviation
SF-36v2	36-item Short-Form Health Survey Version 2
SI	International System of Units
SJC66 / TJC68	Swollen and Tender Joint Count
SmPC	Summary of Product Characteristics
SOPs	Standard Operating Procedures
SPARCC Enthesitis Index and LEI	Spondyloarthritis Research Consortium of Canada Enthesitis Index and Leeds Enthesitis Index
SSZ	sulfasalazine
STAT	signal transducer and activator of transcription
SUSARs	suspected unexpected serious adverse reactions
TB	Tuberculosis
TBNK	T and B lymphocyte and natural killer
TDC	Tender dactylitis count
TEAEs	Treatment-Emergent Adverse Events
Tgras	transgenic
TNF-α	tumor necrosis factor α
TYKs	tyrosine kinases
UC	Ulcerative Colitis
UGTs	uridine 5'-disphosphate glucuronosyltransferases
ULN	upper limit of normal
vfPBMCs	viably frozen peripheral blood mononuclear cells
VHP	Voluntary Harmonisation Procedure
VL	Viral load
VLDA	Very Low Disease Activity
WPAI-PsA	Work Productivity and Activity Impairment for Psoriatic Arthritis

1. INTRODUCTION

1.1. Background

Psoriatic arthritis (PsA) is an inflammatory joint disease associated with psoriasis and characterized by heterogeneous musculoskeletal phenotypes that involve multiple domains including the peripheral joints, axial skeleton, tendon and ligament insertion sites (enthesitis) and digits (dactylitis). PsA occurs in approximately 30% of psoriasis patients {Gladman 2005}. In the majority of cases (75%) psoriasis precedes joint disease, but in some cases (15%) the onset is synchronous and in 10% arthritis precedes psoriasis. In the latter, unrecognized psoriasis may be found or there may be a history of widespread guttate psoriasis in childhood or a strong family history {Ritchlin 2017}.

PsA occurs with equal frequency in males and females. The arthritis in PsA commonly involves distal joints and has the tendency to distribute in a ray pattern where all the joints of a single digit are more likely to be affected. The presence of erythema over affected peripheral joints, asymmetrical spinal involvement, and enthesitis are also typical features of PsA {Gladman 2005}. PsA belongs to the group of spondyloarthropathies with spondylitis being present in up to 40% of patients. The extra-articular features observed in PsA are similar to other spondyloarthropathies including mucous membrane lesions, iritis, urethritis, diarrhea and aortic root dilatation, and association with Human Leukocyte Antigen B27 (HLA-B27) {Gladman 2005}.

First-line treatment traditionally consists of NSAIDs and csDMARDs such as sulfasalazine (SSZ), methotrexate (MTX) and leflunomide (LEF). These drugs remain a mainstay of therapy where there is limited access to biological agents {Gossec 2012}. The arrival of anti-tumor necrosis factor (anti-TNF) agents over a decade ago dramatically increased the treatment armamentarium for PsA leading to improved outcomes for both skin and joint disease {Gladman 2007, Mease 2006}. Nevertheless, anti-TNF agents do not work in all patients and response may diminish over time, partly because of immunogenicity {Mease 2013}. Novel biologic agents with different mechanisms of action that target the interleukin(IL)-23 and IL-17 pathways that promote skin and joint inflammation as well as oral agents including janus kinase (JAK) inhibitors and the phosphodiesterase E4 inhibitor, apremilast, have recently become available as therapeutic options for PsA as well {Ritchlin 2016}.

Several key cytokines in the IL-23 / IL-17 pathways promote skin and joint inflammation through signaling via the JAK pathway. Activated JAKs recruit and activate signal transducer and activator of transcription (STATs) which in turn drive gene transcription {O'Shea 1997}. In December 2017, tofacitinib (Xeljanz®) became the first JAK inhibitor to receive Food and Drug Administration (FDA) approval for the treatment of adult patients with PsA. Tofacitinib is a small molecule, has strong binding affinity for JAK1 and JAK3, and weaker affinity for JAK2. The extensive pre-clinical and clinical development programs demonstrated its mechanisms of action via anti-inflammatory and immunosuppressive effects. The drug proved to be efficacious in treating the signs and symptoms of PsA. However, the observed side effects and risk profile of tofacitinib are similar to those of several existing anti-rheumatic agents with cytopenias, elevated

levels of liver function enzymes, increased total cholesterol levels, with increase in LDL typically exceeding those for HDL, and increased risk for infections including serious and opportunistic infections. At higher doses, tofacitinib treatment was associated with anemia, which is thought to be linked to inhibition of JAK2 {Gladman 2017, Mease 2017a, Mease 2017b}.

While the pan-JAK inhibitor tofacitinib has shown an early onset of action and long-term efficacy in PsA, limitations of therapy include side effects potentially mediated by its effect on JAK2 and JAK3. This highlights the need for more selective and targeted therapies with improved immunomodulatory and hematologic effects. JAK1 is thought to be an integral part of PsA pathogenesis due its role in transmitting inflammatory cytokine signaling. Hence, targeted inhibition of JAK1 has great potential for the treatment of PsA with an improved safety and side effect profile.

1.2. Filgotinib

1.2.1. General Information

Janus kinases are intracellular cytoplasmic tyrosine kinases (TYKs) that transduce cytokine signaling from membrane receptors through STAT to the nucleus of cells. JAK inhibitors block the signaling of various cytokines, growth factors, and hormones, including the pro-inflammatory cytokine IL-6. Four different types of JAKs are known, JAK1, JAK2, JAK3, and TYK2 which co-interact with different sets of membrane receptors. Inhibition of JAKs is a promising therapeutic option for a range of inflammatory conditions including RA, UC, and Crohn's disease (CD).

Filgotinib (GS-6034, formerly GLPG0634) is a potent and selective inhibitor of JAK1. The compound has shown good preliminary efficacy in PsA {Mease 2018}, ankylosing spondylitis {van der Heijde 2018}, RA and CD patients in Phase 2 (filgotinib IB). In a Phase 3 RA study with subjects who failed prior biologic therapy, filgotinib achieved all primary and key secondary endpoints {Genovese 2018}. Additionally, filgotinib is currently under assessment in ongoing Phase 3 RA, UC, CD studies (clinicaltrials.gov).

In humans, filgotinib is metabolized to form one major active metabolite GS-829845 (formerly G254445). Though the potency of this metabolite is lower than the parent molecule, the overall exposure and peak plasma concentration in humans is higher than seen in all tested animal species. As a consequence, dedicated pharmacology and toxicology studies have been performed with GS-829845. Results from pharmacodynamics (PD) testing in healthy volunteers suggest that the clinical activity of filgotinib could result from the combination of the parent molecule and the metabolite.

For further information on filgotinib, refer to the current investigator's brochure (IB) for filgotinib.

1.2.2. Preclinical Pharmacology and Toxicology

Filgotinib and its metabolite, GS-829845 have been extensively characterized in nonclinical studies. This program includes cellular assays demonstrating potency and selectivity of the compound against JAK1; efficacy studies in rats and mice; repeat dose toxicity studies (up to 26 weeks in the rat and 39 weeks in the dog), *in vitro* and *in vivo* safety pharmacology and genetic toxicology studies, and reproductive toxicology studies in rats and rabbits. Additional toxicology studies conducted include phototoxicity studies and dose-range finding studies in support of a definitive rat juvenile toxicity study and a 6 month carcinogenicity study in transgenic (TgrasH2) mice. A 2-year rat oral carcinogenicity study as well as the pre- and post-natal development toxicity study in rats were completed.

1.2.2.1. Primary and Secondary Pharmacology

Filgotinib is an adenosine triphosphate (ATP)-competitive inhibitor of JAK1. It is highly selective for inhibition of JAK1 over 451 other kinases evaluated *in vitro*. In cellular assays, it inhibits JAK / STAT-driven processes with half maximal inhibitory concentration (IC_{50}) values from 179 nM onwards. In human whole blood, JAK1 is inhibited by filgotinib with an IC_{50} of 629 nM and exhibits approximately 30-fold selectivity over JAK2. Filgotinib demonstrated significant efficacy in the rat collagen-induced arthritis (CIA) model as well as in the mouse dextran sulphate sodium (DSS)-induced colitis model.

Metabolite GS829845 exhibits a similar JAK1 selectivity profile but is approximately 10 to 20-fold less potent than the parent filgotinib in *in vitro* assays. GS-829845 was as effective as filgotinib in the rat CIA model, but at doses that required a 10-fold higher exposure.

1.2.2.2. Safety Pharmacology

Filgotinib and GS-829845 had no effects on the respiratory system and central nervous system (CNS) up to respectively 40 and 5-fold the exposure in RA subjects given filgotinib 200 mg once daily.

Filgotinib and GS-829845 had no relevant effects on cardiovascular parameters (human ether-a-gogo related gene [hERG] and dog telemetry studies), apart from a slight non-adverse increase in heart rate and arterial pressure with GS829845 at exposures 7fold that of the C_{max} in subjects with RA treated with 200 mg once daily filgotinib. There were no relevant effects on ECG and QT.

1.2.2.3. Nonclinical Absorption, Distribution, Metabolism, and Excretion (ADME)

Filgotinib demonstrates good oral bioavailability in mice, rats, dogs, and minipigs but less in monkeys. Plasma protein binding is low (<70%) in all species, including humans. The PK of filgotinib is generally dose proportional without gender differences. No accumulation occurs with repeated dosing. The mean terminal half-life after oral administration is 4 and 5 hours (h) in rats and dogs, respectively.

In the rat, filgotinib showed a rapid and even distribution throughout the body. High concentrations were observed only in the gastrointestinal (GI) tract and urinary bladder. Filgotinib does not penetrate into CNS tissues. The distribution of filgotinib indicates some affinity for melanin-containing tissues.

Excretion is nearly complete within 72 h (mouse), 24 h (rat) and 48 h (dog) post-dosing. In the mouse, an average of 54.0 and 37.7% of the administered radioactivity was excreted in feces and urine, respectively. In the rat, fecal and urinary excretion accounted for 40% and 59% of the administered dose, respectively. In bile-duct cannulated rats bile secretion of about 15%. In the dog, fecal excretion was the primary route of excretion, accounting for 59% of the administered dose, with urinary excretion accounting for 25%.

In vitro metabolism studies in all species revealed one major metabolite (GS-829845). The formation of GS-829845 is mediated by carboxylesterases (CES) and is not dependent on cytochrome P450 (CYP).

In vitro experiments have shown that drug-drug interactions with filgotinib and GS-829845 are unlikely. There is no inhibition or induction of CYPs or uridine 5'-disphosphate glucuronosyltransferases (UGTs), and no relevant inhibition of key drug transporters, including the organic anion transporters (OATs) involved in the renal elimination of MTX, by filgotinib or GS-829845.

1.2.2.4. Nonclinical Toxicology

In repeat oral dose toxicity studies in both rats and dogs, the primary target tissues identified for filgotinib were the lymphoid tissues which are expected based on the pharmacology of JAK inhibition. Additional filgotinib-related findings were observed in the male reproductive organs of both species, and in the incisor teeth of rats only. Effects on the lymphoid system were fully reversible. Testicular toxicity demonstrated partial reversibility; however, sperm counts remained low. A dose of 200 mg / day of filgotinib results in an estimated mean clinical area under the curve (AUC) of 2.80 µg·h / mL, which represents an exposure margin of 2.3, 1.8, and 3.4-fold when considering the mean AUC in male dogs at the no-observed-effect-levels (NOELs) in the 26 week and 39 week chronic toxicity studies, and the 39 week targeted exposure toxicity study, respectively.

GS-829845 related findings in general repeat dose toxicity studies were similar to those of the parent filgotinib; however, no testicular toxicity was noted following administration of GS-829845.

Filgotinib and GS-829845 were non-genotoxic when evaluated in the bacterial mutagenicity assay, the *in vitro* mouse lymphoma mutagenicity assay, and the rat bone marrow micronucleus assay.

In embryofetal development studies, filgotinib and GS-829845 caused embryolethality and teratogenicity in rats and rabbits at exposures similar to the human exposure at 200 mg once daily of filgotinib in subjects with RA. Administration of filgotinib did not affect female fertility, but impaired fertility was observed in male rats at exposures approximately 15-fold the human exposure at 200 mg of filgotinib in subjects with RA. GS-829845 did not have any effects on fertility parameters in either male or female rats.

In an in vitro phototoxicity study in 3T3 cells, the metabolite GS-829845 was positive for phototoxic potential and results with filgotinib were equivocal. A follow-up *in vivo* rat phototoxicity assay revealed a lack of phototoxic potential for both compounds.

1.2.3. Clinical Trials of Filgotinib

Comprehensive data from the Phase 1 and 2 programs are available to support development into Phase 3. An overview of exposure and clinical studies conducted with filgotinib is available in the IB.

Phase 2 Filgotinib PsA Study GLGP0634-CL-224 (EQUATOR)

The EQUATOR study was a randomized, double-blind, placebo controlled Phase 2 trial that enrolled adults with active moderate to severe PsA fulfilling Classification Criteria for Psoriatic Arthritis (CASPAR), active or documented history of plaque psoriasis, and an inadequate response or intolerance to at least one csDMARD. Subjects were randomized to receive either placebo or filgotinib 200 mg once daily for 16 weeks. The primary objective of the study was to evaluate efficacy of filgotinib compared to placebo at Week 16.

The percentage of ACR20 responders was statistically significantly higher in filgotinib group at Week 16 compared to placebo. Subjects with previous TNFi therapy had a similar ACR20 response compared to the rest of the study population. The percentage of ACR50 and 70 responders was also statistically significantly higher at Week 16 compared to placebo.

A dose response was observed for all three parameters. Starting at Week 1 response was observed for ACR20 and ACR50 in the filgotinib group and remained statistically significantly superior to placebo through Week 16.

Subjects receiving filgotinib also demonstrated significantly higher clinical efficacy compared to placebo at Week 16 with additional PsA assessments including Disease Activity in Psoriatic Arthritis (DAPSA) score, Psoriatic Arthritis Response Criteria (PsARC) response, PASDAS, and SPARCC Enthesitis Index. The filgotinib group achieved improvement in skin manifestations of disease as demonstrated by the PASI75 score and the pruritus numeric rating scale, both of which were statistically significantly better than placebo at Week 16.

Patient reported outcomes including the HAQ-DI, FACIT-Fatigue, and PsA related pain intensity also improved with filgotinib at Week 16 compared to placebo.

Safety analysis showed similar proportions of filgotinib and placebo recipients had at least one treatment-emergent AE; 37 (57%) for filgotinib, and 39 (59%) for placebo. Six subjects had an event that was grade 3 or 4. The most frequently occurring events were nasopharyngitis and headache, occurring at similar proportions in each group. One serious treatment-emergent AE was reported in each group (pneumonia [filgotinib] and hip fracture after a fall [placebo]). The SAE of pneumonia was a fatal event. No gastric perforations, malignancies, lymphomas, venous thromboembolic events, opportunistic infections, or cases of active tuberculosis (TB) were reported. There was one case of herpes zoster confined to a single dermatome in the filgotinib group. The incidence of infections was similar between the two groups.

Phase 3 Filgotinib Rheumatoid Arthritis Study GS-US-417-0302 (FINCH 2)

FINCH 2 was a randomized, double-blind, placebo-controlled, add-on, Phase 3 study in adult male and female subjects with active RA despite csDMARD(s) therapy (i.e. MTX, hydroxychloroquine, sulfasalazine, leflunomide) who had an inadequate response or were intolerant to at least 1 bioDMARD. Subjects were randomized 1:1:1 to receive once daily filgotinib 200 mg, filgotinib 100 mg, or placebo for 24 weeks all in the context of a stable dose of permitted csDMARD(s). The primary endpoint was the proportion of subjects who achieved an ACR20 response at Week 12.

At Week 12, an ACR20 response was achieved by significantly more subjects receiving filgotinib 200 mg or 100 mg than placebo (66.0%, 57.5% and 31.1%, respectively; both $p<0.001$). The reduction from Baseline in HAQ-DI at Week 12 was greater in the filgotinib 200 mg and 100 mg groups compared to the placebo group (-0.55 and -0.48 vs -0.23, respectively; both $p<0.001$). Other key secondary endpoints, including SF-36v2 and FACIT-Fatigue, were also met at both filgotinib doses.

The safety profile was consistent with data from the Phase 2 studies with filgotinib. AE rates were similar for filgotinib 200 mg, filgotinib 100 mg and placebo groups (69.4% and 63.4% vs 67.6%, respectively) as were rates of serious adverse events (SAEs) (4.1%, 5.2% and 3.4%, respectively. There were 4 cases of uncomplicated herpes zoster (2 in each filgotinib group). There was one non-serious AE of retinal vein occlusion in the filgotinib 200 mg group; no other venous thrombotic events were reported. Two adjudicated major adverse cardiovascular events (MACEs) were reported: one subarachnoid hemorrhage in the placebo group and one myocardial ischemia in the filgotinib 100 mg group. There were no cases of opportunistic infection / active TB, malignancy, GI perforation or death.

1.3. Information about Humira® (adalimumab)

For information on the study drug adalimumab being used as an active comparator, refer to the current package insert.

1.4. Rationale for This Study

Therapeutic options for the treatment of PsA have increased dramatically over the past 15 years resulting in markedly improved outcomes for skin and joint disease {Gladman 2007, Mease 2006}. The arrival of anti-TNF agents represented a major treatment advance because these therapies are very effective for skin and all of the musculoskeletal domains of PsA. Despite of significant uptake in the use of anti-TNF agents, tolerability due to allergic and autoimmune reactions, loss of response due to immunogenicity and increased risk of infections / opportunistic infections remain problematic{Mease 2013}. Agents with different mechanisms of action that target the IL-23 / IL-17 pathways have recently become available. Use of these biological parenterally administered agents has led to marked skin clearance, while musculoskeletal symptoms improvement, the effect observed is similar to that with anti-TNF agents. Apremilast, an oral inhibitor of phosphodiesterase 4 (PDE4) offers modest response in the skin and joint symptoms with few safety signals. Therefore, there is still a need for simple, orally administered agents with novel and targeted mechanisms of action that can effectively improve PsA outcome in all of its domains, and which are well-tolerated and have an acceptable safety profile.

Tofacitinib, an orally administered JAK1 / JAK3 inhibitor, is approved for use in patients with PsA based on the data from two Phase 3 studies in subjects with PsA. In the Phase 3 study evaluating tofacitinib versus placebo in subjects with active PsA and previous inadequate response to TNF inhibitors, the ACR20 responses were 50% with the 5 mg dose of tofacitinib as compared with 24% with placebo ($p<0.001$) after 3 months of treatment. In the Phase 3 study evaluating tofacitinib versus placebo and adalimumab in patients with active PsA and inadequate response to csDMARDs, the ACR20 response rate at month 3 was 50% in the 5 mg tofacitinib group as compared with 33% in the placebo group ($p = 0.01$). Safety results were similar across the two studies in regards to the number and category of AEs. Both studies reported cases of herpes zoster, serious infections and malignancy in the subjects exposed to tofacitinib {Gladman 2017, Mease 2017a}.

The JAK1 selective inhibitor filgotinib targets an intracellular tyrosine kinase dysregulated in subjects with inflammatory disorders including PsA. Filgotinib is a small molecule for oral daily administration that demonstrated clinical efficacy in treating the signs and symptoms of active PsA in a Phase 2 study as well as other inflammatory disorders including RA.

1.4.1. Rationale for Study Design

Study GS-US-431-4566 is a randomized, double-blind, placebo and adalimumab-controlled study evaluating the efficacy and safety of 2 doses of filgotinib administered once daily in subjects with active PsA despite previous non-biologic DMARD therapies: csDMARDs, apremilast, and / or NSAID(s). The study consists of 2 parts:

- Part 1: The Main Study, is from Screening through the Week 16 Visit
- Part 2: LTE immediately follows Part 1 and starts after the Week 16 Visit continuing for 2 years
- Total study duration is ~ 2.25 years.

The objectives of the study are to evaluate the effect of filgotinib compared to placebo and adalimumab on the signs and symptoms, physical function, and quality of life in PsA. Safety and tolerability of filgotinib will also be assessed.

Treatment duration of 12 weeks to assess the primary endpoint is considered optimal to evaluate the potential benefit of filgotinib on a variety of musculoskeletal symptoms of PsA. The effect of filgotinib on the arthritis component is expected to be fast (in previous studies with filgotinib in RA, ACR20 plateaued at Week 8). However, the effect on enthesitis and dactylitis requires longer duration of treatment as observed in recently published studies with other compounds.

The duration of placebo will be limited. All subjects in the placebo arm will be reallocated in a blinded manner 1:1 to 100 mg or 200 mg of filgotinib at Week 16. Given the slowly progressive nature of PsA, 16 weeks of placebo on accepted background therapy is considered both clinically and ethically appropriate and allows an acceptable time period in which to assess initial response to therapy. The use of placebo is critical in evaluating subject reported and subjective outcomes, which can be highly variable and influenced by placebo therapy. The placebo effect is well-established in PsA studies and inclusion of the placebo arm is critical to evaluation of the overall risk-benefit profile of added filgotinib therapy. Finally, the provision of best supportive care in the context of the trial, as well as the limited duration and eventual opportunity for subjects to transition to filgotinib, make the use of placebo ethically acceptable for the specified duration.

This study includes an active comparator, adalimumab, a monoclonal antibody directed against tumor necrosis factor α (TNF-α). The inclusion of the active comparator will allow comparison of the efficacy and safety of filgotinib to an approved and frequently prescribed product indicated for use in this patient population.

The study eligibility criteria are consistent with those of recent clinical trials evaluating novel investigational treatments for PsA. Subjects should meet the CASPAR criteria for PsA. Subjects are required to have active disease defined as ≥3 swollen and ≥3 tender joints at both Screening and Day 1 Visits. In addition, subjects are required to have a history of or active psoriasis lesion. The study duration of ~2.25 years allows sufficient time for demonstrating the safety and tolerability of therapy, reduction in disease activity, and confirmation that clinical benefit is sustained over time.

1.4.1.1. Rationale for Outcome Measures

The ACR responses, MDA, and PASDAS are considered reliable measures of response to treatment and disease activity in subjects with PsA. The psoriasis disease activity will be assessed by the PASI50, PASI75, PASI90, PASI100 and PhGAP. Psoriatic nail involvement will be recorded by using the mNAPSI. Several other disease activity measures will be assessed including SPARCC Enthesitis Index and LEI (for enthesitis), LDI (for dactylitis), CCI [redacted], and PhGADA.

Assessing quality of life (measured by the HAQ-DI, FACIT-Fatigue, SF-36v2, PsAID-12, EuroQol 5 Dimensions with 5 Levels (EQ-5D-5L), and PGAPI) at the Day 1 Visit and during the course of study treatment provides insight into the effects on modifying PsA disease course and impact on daily life. Assessing the change in economic impact (WPAI-PsA), and Healthcare Resource Utilization Questionnaire (HCRU)) of PsA over the course of the study provides insight into the subject's ability to work and other daily activities as well as the impact on the burden of healthcare resources.

1.4.2. Rationale for Dose Selection

Enrolled subjects will be randomized to receive filgotinib (100 mg or 200 mg), active comparator (adalimumab), or placebo. The doses of filgotinib chosen for evaluation in this study, 100 mg and 200 mg once daily, are supported by a combination of safety and efficacy data from Phase 1 and 2 studies in the clinical development program, and the known dose-pSTAT1 inhibition relationship of filgotinib.

In two Phase 2a studies in subjects with RA (Study GLPG0634-CL-201 and -202), dosing with filgotinib was well tolerated and achieved a high level of efficacy at a 200 mg daily dose (ACR20 response of 75-92% at Week 4). Administration of a higher filgotinib dose (300 mg) did not demonstrate greater efficacy, therefore, the highest dose to be tested in this study will be 200 mg once daily. In two Phase 2b studies, filgotinib at daily doses of 50 mg, 100 mg, or 200 mg, administered in addition to a background therapy with MTX (GLPG0634-CL-203) or as monotherapy (GLPG0634-CL-204) was shown to be safe and efficacious in subjects with moderately to severely active RA who had an inadequate response to MTX alone. In the Phase 2 PsA study (GLPG0634-CL-224), filgotinib 200 mg once daily was well tolerated and achieved a high level of efficacy at a 200 mg daily dose as well (ACR20 response rate of 80% at Week 16).

Exposure-response analysis based on data from all Phase 2 studies indicated a dose-dependent increase in efficacy (ACR20 / 50 / 70, Disease Activity Score 28 (DAS28) [C-reactive protein (CRP)]), with a plateau at the 200 mg total daily dose on the dose-response curve. Additionally, in Study GLPG0634-CL-203, no statistically significant difference in efficacy was observed at 200 mg daily dose, administered as 200 mg once daily or 100 mg twice daily. These results are consistent with the relationship observed between filgotinib exposures and pSTAT1 activation (ex-vivo) following single and multiple filgotinib doses, where maximal inhibition of pSTAT1 (~78%) was achieved at or above 200 mg total daily dose and intermediate inhibition (~47%) at 100 mg {Namour 2015}.

Safety data collected across Phase 2 clinical studies showed no dose-dependent trends in the incidence of AEs or SAEs, including infections, or laboratory abnormalities with the exception of a numerical increase in select gastrointestinal AEs (e.g. nausea, vomiting, abdominal pain, and upper abdominal pain). This numerical increase was observed in the 200 mg compared to the 100 mg dose. However, the overall frequency was low and clinical relevance is unknown. Filgotinib, administered at a dose of 100 mg or 200 mg daily, was found to be safe and well tolerated. The safety profile was consistent with that observed for an immunomodulatory compound administered to subjects with RA.

Overall, the 100 mg and 200 mg once daily dosing regimens have been proposed based on the known dose-pSTAT1 inhibition relationship of filgotinib and the clinical experience (safety and efficacy) with PsA and RA subjects in Phase 2 studies. Inclusion of two doses in the proposed Phase 3 trials will enable establishment of an appropriate nominal dose for the treatment of PsA and determine the regimen with the most favorable risk / benefit profile in these populations.

1.5. Risk / Benefit Assessment for the Study

As of June 2018, 6605 subjects have received filgotinib either as single doses or multiple doses, and 1278 subjects have received daily filgotinib for >1 year. In general, filgotinib has been safe and well tolerated in all populations studied. In addition to PsA, large Phase 3 programs in RA, CD and ulcerative colitis (UC) are currently ongoing as well.

Nonclinical studies in rats and dogs identified the testes and lymphoid tissue as target organs for filgotinib in long term repeat-dose toxicity studies. In both species, histopathological changes in the testes included germ cell depletion and degeneration, with reduced sperm content and increased cell debris in the epididymis and reduction in fertility in rats. The dog was determined to be the most sensitive species. A dose of 200 mg / day of filgotinib results in an estimated mean clinical AUC of 2.8 μg·h / mL, which represents an exposure margin of 2.3, 1.8, and 3.4-fold when considering the mean AUC in male dogs at the NOELs in the 26 week and 39 week chronic toxicity studies, and the 39 week targeted exposure toxicity study, respectively. Decreased lymphocytes observed in nonclinical studies have not been shown in clinical studies.

Filgotinib has shown an increased risk of embryofetal malformations at exposures similar to human doses; the use of highly effective contraception in the subject population will be implemented in the study to mitigate this risk.

No clinically relevant impact on cardiovascular parameters (including vital signs and ECG), respiratory or neurologic function has been observed in Phase 1 and 2 trials of filgotinib, including a dedicated Phase 1 study to evaluate the effect of filgotinib on the QT / QTc interval in healthy subjects. The QT study evaluated filgotinib at doses of 200 mg and 450 mg; neither dose led to prolongation in the QTc interval or was associated with clinically significant ECG changes. In Phase 2 trials in RA, filgotinib was well tolerated. In the RA studies (including the open label extension DARWIN 3), infections were reported more commonly in the filgotinib groups, including serious infections leading to hospitalization, and even death. The most common system organ classes with AEs were infections and infestations, and GI disorders. Dose dependent decreases in the Phase 2b studies were observed in mean neutrophil counts and platelet counts (but mean changes in both remained within normal laboratory reference ranges) and there were no decreases in lymphocytes or lymphocyte subsets. Hemoglobin levels slightly improved (increased) with filgotinib treatment, confirming that no anemia was induced. Mild and clinically insignificant serum creatinine increases were noted in both Phase 2b studies, with stabilization by Week 24. Neutrophil decreases (in the RA population) and a potential increased risk of infection may be considered risks consistent with the mechanism of JAK inhibition.

Overall clinical findings and laboratory changes are consistent with selective JAK1 inhibition and based on Phase 2 data the expected benefit of using filgotinib as proposed in this study is considered to outweigh any associated risks.

Adalimumab is a TNFα inhibitor that is indicated and commonly used in the target population of this trial with well-established safety and efficacy profile (Humira (US) Package Insert, Humira (EU) Summary of Product Characteristics (SmPC)).

The dose and duration of adalimumab treatment proposed in this study are in line with posology approved globally (Humira US Package Insert, Humira EU SmPC).

Risks associated with the use of adalimumab are well characterized, and are described in approved local product information. Adalimumab is associated with an increased risk for developing serious infections that may lead to hospitalization or death. Opportunistic infections due to bacterial, mycobacterial, invasive fungal, viral, parasitic, or other opportunistic pathogens have been reported with TNFα inhibitors. Reactivation of latent TB has been reported. All subjects will be tested for TB before study start as outlined in the exclusion criteria and will be carefully monitored for signs and symptoms of infection during and after the study. Study drug will be discontinued for serious infections as outlined in Section 3.5. An increase of nonmelanoma skin cancers, hematologic cancers and a potential increase of other cancers have been reported with use of TNFα inhibitors. Subjects will undergo regular assessments, including physical examination and hematological assessments.

TNFα inhibitors are commonly used as first line therapy in this patient population. Their efficacy has been well established. Overall, the benefit of using adalimumab as proposed in this study is considered to outweigh any associated risks.

An independent Data Monitoring Committee (DMC) appointed to monitor the study (with the initial DMC data review after the first 100 subjects across the program, Study GS-US-431-4566 and Study GS-US-431-4567, complete 12 weeks of treatment) will provide an additional level of risk mitigation. The overall risk / benefit balance of this study is considered favorable. For additional information about the risks of filgotinib, reference is made to the investigator brochure.

1.6. Compliance

This study will be conducted in compliance with this protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

2. OBJECTIVES

The primary objective of this study is:

- To evaluate the effect of filgotinib compared to placebo in active PsA as assessed by the ACR20 response at Week 12

The secondary objectives of this study are:

- To evaluate the effect of filgotinib on core domains of PsA (e.g. peripheral arthritis, psoriatic skin disease, enthesitis and dactylitis) as assessed by MDA, VLDA, ACR responses, PASI including BSA responses, SPARCC Enthesitis Index and LEI, LDI, PASDAS, DAPSA, mNAPSI, and PhGAP.
- To evaluate the effect of filgotinib on physical function in active PsA as assessed by HAQ-DI
- To evaluate the effect of filgotinib on fatigue and quality of life in active PsA as assessed by FACIT-Fatigue, SF-36v2, and PsAID-12
- To evaluate the efficacy of filgotinib versus adalimumab in active PsA as assessed by ACR20
- To evaluate the safety and tolerability of filgotinib

CCI [redacted]

3. STUDY DESIGN

3.1. Endpoints

3.1.1. Primary Endpoint

The primary endpoint is the ACR20 response at Week 12.

3.1.2. Key Secondary Endpoints

The key secondary endpoints include:

- ACR50 response at Week 12
- Change from Baseline in HAQ-DI at Week 12
- Change from Baseline in SF-36v2 physical component summary (PCS) at Week 16
- Change from Baseline in LEI at Week 16, in subjects with enthesitis at Baseline
- PASI75 response at Week 16, in subjects with psoriasis covering ≥3% of the BSA at Baseline
- MDA response at Week 16
- Change from Baseline in FACIT-Fatigue at Week 16
- Change from Baseline in LDI at Week 16, in subjects with dactylitis at Baseline

3.1.3. Other Secondary CCI Endpoints

Other secondary CCI endpoints will be evaluated at all scheduled or applicable time points in the Main Study other than the time points that are already specified in the primary and key secondary endpoints.

The other secondary endpoints include:

- Change from Baseline in PASDAS
- MDA response
- VLDA response
- Change from Baseline in DAPSA
- Change from Baseline in PhGAP, in subjects with psoriasis covering ≥3% of the BSA at Baseline

- Change from Baseline in mNAPSI, in subjects with psoriatic nail involvement at Baseline
- Change from Baseline in LEI, in subjects with enthesitis at Baseline
- Change from Baseline in PsAID-12
- PASDAS low disease activity (LDA, i.e. PASDAS ≤3.2)
- PASDAS remission (i.e. PASDAS ≤1.9)
- ACR20 response
- ACR50 response
- ACR70 response
- Change from Baseline in individual components of the ACR response criteria
- Change from Baseline in DAS28(CRP)
- DAS28(CRP) LDA
- DAS28(CRP) remission
- Time to achieve DAS28(CRP) LDA
- DAPSA LDA
- DAPSA remission
- Time to achieve DAPSA LDA
- PsARC response
- Change from Baseline in PASI, in subjects with psoriasis covering ≥3% of the BSA at Baseline
- PASI50 response, in subjects with psoriasis covering ≥3% of the BSA at Baseline
- PASI75 response, in subjects with psoriasis covering ≥3% of the BSA at Baseline
- PASI90 response, in subjects with psoriasis covering ≥3% of the BSA at Baseline
- PASI100 response, in subjects with psoriasis covering ≥3% of the BSA at Baseline
- Change from Baseline in SPARCC Enthesitis Index, in subjects with enthesitis at Baseline

- Change from Baseline in LDI, in subjects with dactylitis at Baseline
- Change from Baseline in tender dactylitis count (TDC), in subjects with dactylitis at Baseline
- Change from Baseline in HAQ-DI
- Change from Baseline in FACIT-Fatigue
- Change from Baseline in SF-36v2 PCS and mental component score (MCS)

CCI

[redacted]

3.2. Study Design

This is a randomized, double-blind, placebo and active-controlled, Phase 3 study in adult male and female subjects with active PsA who have had an inadequate response or intolerance to 1 or more therapies for PsA, such as csDMARDs, apremilast and / or NSAIDs, but have never received a bioDMARD for PsA or psoriasis.

The study consists of two parts, the Main Study which is the Screening Visit through Week 16 (inclusive) and the LTE which is after the Week 16 Visit up to ~2.25 years.

Adult male and female subjects with active PsA will be screened to determine eligibility as per the inclusion and exclusion criteria, see Sections 4.2 and 4.3 respectively. The Screening period will be up to 28 days. Extensions to the screening timeline, exclusively due to imaging, will be considered by the Medical Monitor or designee; approval in writing will be required. Written informed consent must be obtained before any study-related procedures take place. Subjects will be randomized in a 2:2:1:2 ratio to filgotinib 200 mg, filgotinib 100 mg, active comparator (adalimumab), or matching placebo controls administered for up to 16 weeks in a double-blind fashion. The last self-injection of adalimumab (ADA) / PTM is scheduled at 14 weeks. At the

Week 16 Visit, subjects who have not permanently discontinued study drug will continue on to the LTE as follows:

- Those who were assigned to the filgotinib groups will continue on the same study drug assignments
- Those who were assigned to the placebo or active comparator groups will be reassigned 1:1 to filgotinib 100 mg or 200 mg once daily

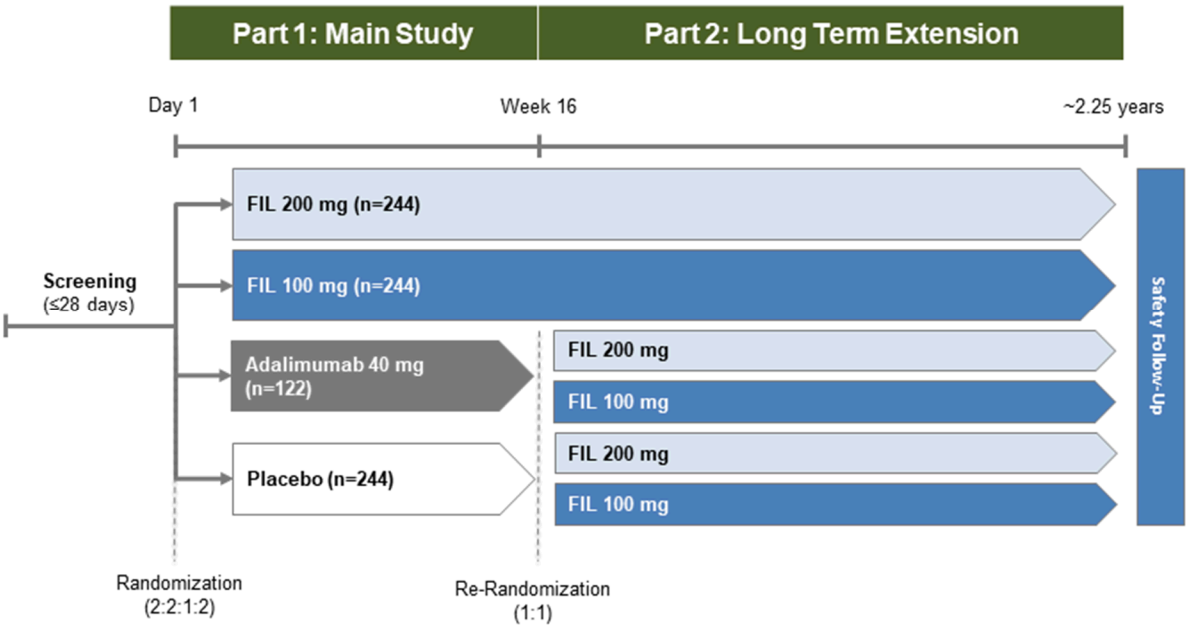
For the first 16 weeks of study participation, subjects who temporarily interrupt or permanently discontinue blinded study drug for any reason are to continue with study visits and assessments through the Week 16 Visit, per Section 3.5, unless the subject withdraws consent, is lost to follow-up, and / or continuation in the study is medically contraindicated, per investigator's judgment. Study drug interruption and discontinuation considerations are outlined in Section 3.5 and include serious infections, inadequate response or loss of response, per investigator judgement. All subjects who permanently discontinue study drug should continue to receive standard of care treatment for their PsA.

Concomitant medications are to remain stable throughout the Main Study; however, after the Week 16 Visit assessments have been completed, investigators may adjust the dose of any of the subject's background medications for management of PsA disease activity, as per Section 5.4.

After all subjects have completed the Week 16 Visit or have permanently discontinued the study prior to Week 16, the treatment assignments will be unblinded to the Sponsor only. The subjects and investigators will remain blinded to individual level treatment assignment.

The assessments planned to be performed at each visit are detailed in the Study Procedures Table (Appendix 2**)**. A schedule of the study design is provided below.

Figure 3-1. Study Design



Four weeks after the subject's final visit (end of study or ET Visit), a Safety Follow-up will be performed via phone for all subjects, unless otherwise required.

3.3. Study Treatments

Approximately 854 subjects will be randomized in a 2:2:1:2 ratio to one of 4 dosing groups.

Dosing groups in the Main Study:

- Filgotinib 200 mg group: filgotinib 200 mg once daily + placebo to match (PTM) filgotinib 100 mg once daily + PTM adalimumab SC injection q2
- Filgotinib 100 mg group: PTM filgotinib 200 mg once daily + filgotinib 100 mg once daily + PTM adalimumab SC injection q2w
- Active comparator group: PTM filgotinib 200 mg once daily + PTM filgotinib 100 mg once daily + adalimumab 40 mg SC injection q2w
- Placebo control group: PTM filgotinib 200 mg once daily + PTM filgotinib 100 mg once daily + PTM adalimumab SC injection q2w

Dosing groups in the LTE:

- Filgotinib 200 mg group: filgotinib 200 mg once daily + PTM filgotinib 100 mg once daily

- Filgotinib 100 mg group: PTM filgotinib 200 mg once daily + filgotinib 100 mg once daily

3.4. Duration of Treatment

Subjects are planned to participate in the study for ~2.25 years: the Main Study for 16 weeks and LTE for 2 years.

3.5. Discontinuation Criteria

3.5.1. Study Drug Interruption Considerations

Study drug interruption should be considered in the following circumstances below. Gilead Medical Monitor should be consulted if the principal investigator believes discussion is warranted.

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree.
- Subject is scheduled for elective or emergency surgery (excluding minor skin procedures under local or no anesthesia); timing of study drug pausing should be determined in consultation with the Gilead Medical Monitor or its designee.
- Any subject who develops a new infection during the study should undergo prompt and complete diagnostic testing appropriate for an immunocompromised individual, and the subject should be closely monitored.

NOTE: During the time of study drug interruption for any of the above, the subject should continue to have study visits as scheduled in Appendix 2 and to take part in procedures and assessments, if deemed medically appropriate by the investigator.

3.5.2. Study Drug Discontinuation Considerations

The Gilead Medical Monitor or its designee should be consulted prior to study drug discontinuation when medically feasible.

Study medication should be permanently discontinued in the following instances:

- Any opportunistic infection
- Any serious infection that requires antimicrobial therapy or hospitalization
- Complicated herpes zoster infection (with multi-dermatomal, disseminated, ophthalmic, or CNS involvement)
- Evidence of active hepatitis C virus (HCV) during the study, as evidenced by HCV RNA positivity

- Evidence of active hepatitis B virus (HBV) during the study, as evidenced by HBV DNA positivity
- Any thromboembolic event that meets SAE reporting criteria
- Uncontrolled disease activity, per the investigator's judgment
- Unacceptable toxicity, or toxicity that, in the judgment of the investigator, compromises the subject's ability to continue study-specific procedures or is considered to not be in the subject's best interest
- Subject request to discontinue for any reason
- Pregnancy during the study
- Discontinuation of the study at the request of Gilead, a regulatory agency or an Institutional Review Board or Independent Ethics Committee (IRB / IEC)
- Subject use of prohibited concurrent therapy may trigger study drug discontinuation; consultation should be made with the Gilead Medical Monitor or its designee
- Laboratory criteria

  a) 2 sequential neutrophil counts <750 neutrophils / mm^3 (International System of Units (SI): <$0.75x10^9$ cells / L)

  b) 2 sequential platelet counts <75,000 platelets / mm^3 (SI: <$75.0x10^9$ cells / L)

  c) 2 sequential values for estimated creatinine clearance <35 mL / min based on the Cockroft Gault Formula

  d) 2 sequential aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevations >3x upper limit of normal (ULN) and ≥1 total bilirubin value >2xULN or accompanied by symptoms consistent with hepatic injury

  e) 2 sequential AST or ALT elevations >5xULN

  While the above lab criteria are for study drug discontinuation, actions should be taken after any of these abnormalities occur at any one time (e.g. a single neutrophil count <750 neutrophils / mm^3 [SI: <$0.75x10^9$ cells / L]) by conducting an unscheduled visit to perform a re-test of the abnormal result within 3 to 7 days (except creatinine, which should be retested 7-14 days apart).

  NOTE: In each case of elevated AST or ALT, there is a need for additional investigations, such as review of ethanol, recreational drug and dietary supplement consumption; testing for acute hepatitis A, B or C infection and biliary tract imaging should be promptly discussed with the study Medical Monitor.

Subjects who permanently discontinue study drug for any reason, including pregnancy, are to receive standard of care treatment for their PsA as determined by the investigator, and those subjects should continue study participation until the Week 16 Visit, if deemed medically appropriate by the investigator.

If there are any questions regarding permanent discontinuation, these should be discussed with the Sponsor or its designee.

3.6. End of Study

End of Study is defined as when the last subject has completed all scheduled dosing (~2.25 years) plus their Safety Follow-up Visit or the study has been terminated.

3.7. Post Study Care

After the subject has completed their study participation, the long-term care of the participant will remain the responsibility of the participant and / or their primary treating physician.

CCI [redacted]

CCI [redacted]

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[redacted]

CCI [redacted]

[redacted]

3.9. MRI Investigation

At capable sites (i.e. qualifying equipment, local regulatory approval, etc.) a subset of subjects (approximately 50 per dosing group) will undergo MRI evaluation with gadolinium. These subjects must provide consent and meet the entrance criteria for MRI in Section 4.4, MRIs with gadolinium of a single hand / wrist will be performed at two time points: Screening and at the Week 16 Visit. Determination of whether to image the subject's right or left hand / wrist will be up to the judgment of the investigator, depending on clinical findings for disease activity at Screening. The same hand / wrist must be scanned for the Week 16 MRI. Subjects may withdraw consent from the MRI investigation at any time during the Main Study.

Subjects who fail the entry criteria of the MRI investigation with the first MRI, or who do not continue onto the Week 16 MRI, may be replaced by consenting additional subjects. Further details of the MRI investigation and procedural requirements will be provided to sites in a separate manual.

CCI [redacted]

[redacted]

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

A sufficient number of subjects will be screened to ensure that ~854 subjects with active PsA will be randomized to one of 4 dosing groups.

4.2. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for participation in this study.

1) Male or female subjects who are 18-75 years of age (19-75 years of age at sites in Republic of Korea, 20-75 years of age at sites in Japan and Taiwan) on the day of signing initial informed consent

2) Meet CASPAR and have a history consistent with PsA ≥6 months at Screening

3) Have active PsA defined as ≥3 swollen joints (from a 66 SJC) and ≥3 tender joints (from a 68 TJC) at Screening and Day 1; these may or may not be the same joints at Screening and Day 1

4) Must have a documented history or active signs of at least one of the following at Screening:

    a) Plaque psoriasis

    b) Nail changes attributed to psoriasis

5) Have had inadequate response or intolerance to ≥1 csDMARD, apremilast and / or NSAID, administered over the course of ≥12 weeks for the treatment of PsA, as per local guidelines / standard of care

6) If continuing csDMARD(s) during the study, subjects are permitted to use only a maximum of 2 of the following drugs and must have been on this treatment for ≥12 consecutive weeks prior to Screening, with a stable dose and route of administration (defined as no change in prescription) for ≥4 weeks prior to Day 1:

    a) MTX oral or SC up to 25 mg / week (must include concomitant use of a folic / folinic acid supplementation as per local standard of care / investigator judgment; MTX use may not be combined with leflunomide during the study)

    b) Leflunomide up to 20 mg once daily orally (may not be combined with MTX during the study)

    c) Sulfasalazine up to 3 g daily orally

d) Hydroxychloroquine up to 400 mg daily or chloroquine up to 250 mg daily

e) Apremilast up to 30 mg twice daily orally

f) Azathioprine up to 200 mg daily orally

g) Cyclosporine up to 300 mg daily

7) If csDMARDs are stopped prior to Day 1, the following washout periods are required:

a) ≥4 weeks prior to Day 1: apremilast, sulfasalazine, azathioprine, MTX, hydroxychloroquine

b) ≥8 weeks prior to Day 1: oral cyclosporine

c) Leflunomide must either have a washout period of ≥8 weeks prior to Day 1 or ≥4 weeks prior to Day 1 if 11 days of standard cholestyramine therapy was completed

8) If taking NSAIDs, dose must be kept stable (defined as no change in prescription) for ≥2 weeks prior to Day 1

9) If taking oral corticosteroids, dose must be ≤10 mg / day of prednisone or equivalent, and be kept at a stable dose (defined as no change in prescription) for ≥4 weeks prior to Day 1

10) If using topical therapies for psoriasis (e.g. topical corticosteroids, coal tar, salicylic acid, vitamin D analogs, retinoids, anthralin, topical calcineurin inhibitors such as tacrolimus) dose must be stable (defined as no change in prescription) ≥2 weeks prior to Day 1

11) Meet one of the following TB Screening criteria:

a) No evidence of active or latent TB, which is defined as having ALL of the following:

i) A negative QuantiFERON® TB-Gold Plus test at Screening

AND

ii) A chest radiograph (views as per local guidelines) taken at Screening or within the 3 months prior to Screening (with the report or films available for investigator review) without evidence of active or latent TB infection

AND

iii) No history of either untreated or inadequately treated latent or active TB infection

b) For subjects with prior latent TB:

i) A completed course of therapy, as per local standard of care, for latent TB (9 months of isoniazid in a location where rates of primary multi-drug resistant TB infections are <5% or an acceptable alternative regimen) WITH a chest X-ray within 3 months prior to or at Screening

In these cases, no QuantiFERON® TB-Gold Plus test (or equivalent assay) need be obtained. A chest radiograph with the report or films must be available for investigator review.

NOTE: Cases falling under category "b" need to be approved in writing by the Sponsor or its designee prior to enrollment in the study. Subjects with currently ACTIVE TB are not allowed in the study, regardless of past or present anti-TB medication use. Subjects with a new diagnosis of latent TB during screening are not allowed in the study until completion of latent TB treatment is documented.

12) Able and willing to sign the informed consent as approved by IRB / IEC. Written consent must be provided before initiating any Screening evaluations. Subjects must have read and understood the informed consent form (ICF), must fully understand the requirements of the study, and must be willing to comply with all study visits and assessments. Subjects who cannot read or understand the ICF may not be enrolled by a guardian or any other individual.

13) Able and willing to perform SC self-injections or have a caregiver able, willing, and available to administer the injections

14) Subjects receiving non-prohibited medication for any reason should be on a stable dose (defined as no change in prescription and stable per investigator judgment) prior to the first administration of study drug on Day 1

15) A negative serum pregnancy test result at the Screening Visit and negative urine pregnancy test result at the Day 1 Visit are required for female subjects of child bearing potential (as defined in Appendix 3)

16) Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in Appendix 3**.**

17) Lactating females must agree to discontinue nursing before the study drug is administered

4.3. Exclusion Criteria

Subjects who meet *any* of the following exclusion criteria are not to be enrolled in this study.

1) Known hypersensitivity to the study drug, the metabolites, or formulation excipients

2) Prior PsA or psoriasis treatment with a bioDMARD

3) Prior exposure to a JAK inhibitor >2 doses

4) Corticosteroid use as follows:

   a) Intra-articular corticosteroids ≤8 weeks of Day 1

   b) Parenteral corticosteroids ≤2 weeks of Day 1

5) Use of any of the following treatments ≤4 weeks of Day 1:

   a) Intra-articular injection of hyaluronate therapies

   b) Oral retinoids (including tazarotene)

   c) Phototherapy (UVA or UVB) with or without psoralens or self-treatment with sunbathing or tanning beds

   d) Potent P-glycoprotein (P-gp) inducers (e.g. carbamazepine, clotrimazole, dexamethasone, phenothiazine, phenytoin, retinoic acid, rifampin, St. John's wort and venlafaxine)

   e) Oral or injectable gold

   f) D-penicillamine

   g) Cytotoxic agents including chlorambucil, cyclophosphamide, nitrogen mustard, or other alkylating agents

6) Any moderately to severely active musculoskeletal or skin disorder other than PsA or plaque psoriasis that would interfere with assessment of study parameters, as per judgment of investigator

   NOTE: Prior history of reactive arthritis or axial spondyloarthritis is permitted if there is documentation of change in diagnosis to PsA or an additional diagnosis of PsA

7) Any history of an inflammatory arthropathy with onset before age 16 years old

8) Active autoimmune disease that would interfere with assessment of study parameters or increase risk to the subject by participating in the study, (e.g. uveitis, inflammatory bowel disease, uncontrolled thyroiditis, systemic vasculitis, transverse myelitis), per judgement of investigator

9) Presence of any extra-articular manifestations typically associated with RA, such as rheumatoid nodules, rheumatoid lung, or other signs / symptoms, as per judgement of investigator

10) Have undergone surgical treatments for PsA, including synovectomy or arthroplasty in >4 joints and / or ≤12 weeks prior to Day 1

11) History of major surgery (requiring regional block or general anesthesia) ≤3 months prior to Screening or planned major surgery during the study

12) Administration of a live / attenuated vaccine ≤30 days prior to Day 1, or planned during the study

13) Participation in any clinical study of an investigational drug / device ≤4 weeks or 5 half-lives prior to Screening, whichever is longer. Exposure to investigational biologics must be discussed with the Sponsor with written approval.

14) History of or current moderate to severe congestive heart failure (New York Heart Association [NYHA] class III or IV), or within the last 6 months, a cerebrovascular accident, myocardial infarction, unstable angina, unstable arrhythmia, new or significant ECG finding at Screening, or any other cardiovascular condition which, in the opinion of the investigator, would put the subject at risk by participation in the study

15) History of malignancy ≤5 years prior to Screening (except for adequately treated basal cell carcinoma or non-metastatic squamous cell carcinoma of the skin or cervical carcinoma in situ, with no evidence of recurrence)

16) History of lymphoproliferative disease or current lymphoproliferative disease

17) History of organ or bone marrow transplant

18) History of gastrointestinal perforation

19) Positive serology for human immunodeficiency virus (HIV) 1 or 2

20) Evidence of active HCV infection. Subjects with positive HCV Antibody (Ab) at Screening, require reflex testing for HCV RNA. Subjects with positive HCV RNA viral load (VL) at Screening will be excluded. Subjects with positive HCV Ab, but negative HCV RNA VL are eligible per investigator judgment, but require ongoing monitoring as outlined in the Study Procedures Table (Appendix 2).

21) Evidence of active HBV infection. Subjects with positive HBV surface antigen (HBsAg) at Screening are excluded from the study. Subjects with positive HBV core Ab and negative HBsAg, require reflex testing for HBV DNA. Subjects with positive HBV DNA at Screening will be excluded. Subjects with positive HBV core Ab, and negative HBV DNA are eligible per investigator judgment, but may require prophylactic treatment in accordance with HBV treatment guidelines / local standard of care and require ongoing monitoring with blood tests for HBV DNA as outlined in the Study Procedures Table (Appendix 2).

22) History of opportunistic infection, or immunodeficiency syndrome, which would put the subject at risk, as per investigator judgment

23) Active infection that is clinically significant, as per judgment of the investigator, or any infection requiring hospitalization or treatment with intravenous anti-infectives ≤60 days of Screening; or any infection requiring oral anti-infective therapy ≤2 weeks of Day 1

24) Currently on any therapy for chronic infection (such as pneumocystis, cytomegalovirus, herpes zoster, and atypical mycobacteria)

25) History of disseminated staphylococcus aureus or disseminated herpes simplex infection

26) History of symptomatic herpes zoster infection ≤12 weeks prior to Screening or have history of disseminated / complicated herpes zoster infection (multi-dermatomal involvement, ophthalmic zoster, central nervous system involvement or postherpetic neuralgia)

27) History of an infected joint prosthesis or other implanted device with retention of the prosthesis or device in situ

28) Current tobacco, alcohol, or substance abuse, per investigator judgement

29) Any known condition or contraindication as addressed in the local labeling for adalimumab that would preclude the subject from participating in this study

30) Active fibromyalgia or other disorder that based on the investigator's opinion would make it difficult to appropriately assess PsA activity for the purposes of this study

31) Any chronic, uncontrolled medical condition, which would put the subject at increased risk during study participation including but not limited to: diabetes, hypertension, morbid obesity, thyroid, adrenal, pulmonary, hepatic, renal, neurological and / or psychiatric disease or other disease of concern, or circumstances which may make a subject unlikely or unable to complete or comply with study procedures and requirements, as per investigator judgement

32) Ongoing suicidal ideation or history of suicide attempt ≤20 years of Screening

33) Significant blood loss (>450 mL) or transfusion of any blood product ≤12 weeks prior to Day 1

34) Central laboratory tests at Screening that meet any of the criteria below:

a) Hemoglobin <8.0g / dL (SI: <80 g / L)

b) White blood cells $<3.0 \times 10^3$ cells / mm^3 (SI: $<3.0 \times 10^9$ cells / L)

c) Neutrophils $<1.5 \times 10^3$ cells / mm^3 (SI: $<1.5 \times 10^9$ cells / L)

d) Lymphocytes $<0.5 \times 10^3$ cells / mm^3 (SI: $<0.5 \times 10^9$ cells / L)

e) Platelets $<100 \times 10^3$ cells / mm^3 (SI: $<100 \times 10^9$ cells / L)

f) ALT or AST ≥1.5x ULN

g) Total bilirubin level ≥1.5x ULN unless the subject has been diagnosed with Gilbert's disease and this is clearly documented

h) Estimated creatinine clearance <40 mL/min based on the Cockroft Gault formula

NOTE: Before subject is considered a screen-failure, out of range lab values may be rechecked one time after consultation with the Sponsor or designee. Written approval must be obtained.

35) Subject is unwilling or unable to follow protocol requirements

4.4. MRI Investigation Eligibility Criteria

4.4.1. MRI Inclusion Criteria:

1) Subject must fulfill criteria for entry to the Main Study

2) Subject must have PsA joint involvement at a minimum in one hand / wrist as confirmed by the investigator at Screening. The same hand / wrist (R or L) should be imaged at all subsequent MRIs, regardless of PsA activity

3) Subject's baseline MRI must fulfill at least one of the below criteria by central reading:

   a) Definitive intra-articular MRI synovitis (PsAMRIS Grade ≥2 in any applicable hand or wrist joint, or PsAMRIS Grade 1 in ≥2 applicable joints)

      OR

   b) Definitive MRI osteitis in any applicable bone

4) An acceptable baseline MRI read and approved by central imaging, on or before the end of the Screening period

4.4.2. MRI Exclusion Criteria

Subjects may still participate in the Main Study / LTE if ineligible for the MRI investigation. Reasons for ineligibility may include, but are not limited to:

1) Inability or medical contraindication for an MRI examination (e.g. presence of a pacemaker, defibrillator, or other contraindicated implanted metallic device, such as anterior interbody cages, aneurysm clip or pedicle screws, severe claustrophobia or weight >350 lbs./158 kg)

2) Metallic fragments embedded anywhere in the body OR pigment-containing tattoos in the area of examination

3) Known or potential risk of adverse reaction to gadolinium-based contrast agents, including but not limited to, allergy or compromised renal function, per investigator judgment

4) Very difficult peripheral intravascular access

4.5. Screen Failures

Subjects who do not enter the study due to administrative reasons (for example, exceeding the screening window due to issues with appointment scheduling or delays in obtaining results of laboratory data) may be rescreened one time.

Subjects who are permitted to rescreen will receive a new screening number and must repeat all screening assessments including the informed consent. Rescreening should not be used to recheck a subject who is likely unsuitable for the study, for example, to check whether their chronically abnormal laboratory test is closer to normal range.

Subjects who do not meet the inclusion / exclusion criteria for entry into the MRI investigation ("MRI screen failures"), should forgo the MRI investigation and continue participation in the Main Study.

5. STUDY DRUG

5.1. Randomization, Blinding and Treatment Codes

An Interactive Voice / Web Response System (IXRS) will be used to manage subject randomization and treatment assignments. It is the responsibility of the investigator to ensure that the subject is eligible for the study prior to enrollment. Randomization scheme for each Main Study's transition to the LTE is outlined in Section 3.2. Study drug assignments either at Baseline or at LTE will be maintained in a blinded fashion within the IXRS.

Subjects and Investigators will be kept blinded to the results of the CRP test at all visits. Sponsor will be blinded to CRP results in the Main Study only, except the Day 1 Visit. T and B lymphocyte and natural killer (TBNK) results will be blinded to subjects and Investigators at all visits.

Blinding of study treatment is critical to the integrity of this clinical trial. CCI [redacted] Individuals in Clinical Packaging and Labeling or Clinical Supply Management who have an Unblinded Inventory Manager role in the IXRS system for purposes of study drug inventory management, and individuals in Pharmacovigilance and Epidemiology (PVE) responsible for safety signal detection, and / or expedited reporting of suspected unexpected serious adverse reactions (SUSARs) to regulatory authorities may be unblinded to individual case data and / or group level summaries. Contract research organization (CRO) biostatisticians and programmers will be unblinded for the DMC data reviews.

5.1.1. Procedures for Breaking Treatment Codes

In the event of a medical emergency where breaking the blind is required to provide medical care to the subject, the investigator may obtain treatment assignment directly from the IXRS system for that subject. Gilead recommends, but does not require, that the investigator contact the Gilead Medical Monitor or designee before breaking the blind. Treatment assignment should remain blinded unless that knowledge is necessary to determine subject emergency medical care. The rationale for unblinding must be clearly explained in source documentation and on the electronic case report form (eCRF), along with the date on which the treatment assignment was unblinded. The investigator is requested to contact the Gilead Medical Monitor or designee promptly in case of any treatment unblinding.

If a subject's treatment assignment is disclosed to the investigator due to a medical emergency, the subject will have study treatment discontinued.

5.2. Description and Handling of Filgotinib and PTM Filgotinib

5.2.1. Formulation of Filgotinib and PTM Filgotinib

Filgotinib is provided as 100 mg and 200 mg strength tablets. Filgotinib tablets, 100 mg and 200 mg, are beige, debossed with "GSI" on one side and "100" or "200" on the other, capsule-shaped, biconvex, film-coated tablets for clinical use. Each tablet contains the equivalent of 100 mg or 200 mg filgotinib free base in the form of filgotinib maleate. In addition to the active ingredient, filgotinib tablets contain the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, fumaric acid, pregelatinized starch, silicon dioxide, magnesium stearate, macrogol / polyethylene glycol (PEG) 3350, polyvinyl alcohol, talc, titanium dioxide, iron oxide yellow, and iron oxide red.

PTM filgotinib tablets, 100 mg and 200 mg, are identical in appearance to the respective active tablets. PTM filgotinib tablets contain the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, macrogol / PEG 3350, polyvinyl alcohol, talc, titanium dioxide, iron oxide yellow, and iron oxide red. For the purpose of the LTE, PTM filgotinib tablets will only be utilized for the maintenance of the Main Study's treatment assignment blind, and not as a comparator treatment to active filgotinib.

5.2.2. Packaging and Labeling of Filgotinib and PTM Filgotinib

Filgotinib tablets, 100 mg and 200 mg, and PTM filgotinib tablets, 100 mg and 200 mg, are packaged in white, high density polyethylene (HDPE) bottles. Each bottle contains 30 tablets, silica gel desiccant and polyester packing material. Each bottle is enclosed with a white, continuous thread, child-resistant polypropylene screw cap fitted with an induction-sealed, aluminum-faced liner.

Sufficient quantities of filgotinib tablets, 100 mg and 200 mg, and PTM filgotinib tablets to complete the entire study will be shipped to the investigator or qualified designee from the Gilead Supply Management Team (or its designee).

Study drugs to be distributed to participating sites shall be labeled to meet applicable requirements of the U.S. FDA, the EU Guideline to Good Manufacturing Practice – Annex 13 (Investigational Medicinal Products), the Ministerial Ordinance on Good Clinical Practice for Drugs in Japan, and / or other local regulations, as applicable.

5.2.3. Storage and Handling of Filgotinib and PTM Filgotinib

Filgotinib tablets and PTM filgotinib tablets should be stored at controlled room temperature of 25°C (77°F); excursions are permitted between 15°C and 30°C (59°F to 86°F). Storage conditions are specified on the label.

Until dispensed to the subjects, all drug products should be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability of the study drug and to ensure proper product identification, the drug product should not be stored in a container other than the container in which they are supplied. Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure when handling.

5.2.4. Dosage and Administration of Filgotinib and PTM Filgotinib

Filgotinib tablets, 100 mg or PTM and 200 mg or PTM will be administered once daily with or without food. Each subject should be given instructions to maintain approximately the same daily time of administration to ensure similar dosing interval is maintained between study drug doses.

For missed dose(s) of study medication, subjects should be instructed to take the missed dose(s) of study medication as soon as possible during the same day. If the missed dose is not taken on the original day, subjects should be cautioned not to double the next dose with the missed dose of study drug under any circumstances. In those cases, the missed dose should be returned to the study drug bottle.

5.3. Description and Handling of Adalimumab and PTM Adalimumab

5.3.1. Formulation of Adalimumab and PTM Adalimumab

Adalimumab is commercially sourced. Information regarding the formulation can be found in the current prescribing information.

PTM adalimumab will be manufactured by Gilead Sciences, Inc. (GSI) to match the presentation of adalimumab. It will be visually identical to the adalimumab, but will contain no active ingredient. PTM adalimumab for SC injection is formulated as a sterile, aqueous buffered solution in a single-use prefilled syringe. The buffered solution contains sucrose, acetic acid, and sodium acetate at pH 5.0.

5.3.2. Packaging and Labeling of Adalimumab and PTM Adalimumab

Adalimumab and PTM for SC injection will be supplied in clear, single-use prefilled syringe. Each syringe delivers 40 mg of drug product or matching placebo.

Study medication to be distributed to participating sites shall be labeled to meet applicable requirements of the US FDA, EU Guideline to Good Manufacturing Practice – Annex 13 (Investigational Medicinal Products), the Ministerial Ordinance on Good Clinical Practice for Drugs in Japan, and / or other local regulations, as applicable.

5.3.3. Storage and Handling of Adalimumab and PTM Adalimumab

Adalimumab and PTM should be stored under refrigeration between 2°C to 8°C (36°F to 46°F), protected from light and should not be frozen. Storage conditions are specified on the label.

Until dispensed to the subjects, all drug products should be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability of the study drug and to ensure proper product identification, the drug product should not be stored in a container other than the container in which they are supplied. Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure when handling.

5.3.4. Dosage and Administration of Adalimumab and PTM Adalimumab

Adalimumab or PTM adalimumab will be self-administered by the subject or caregiver as specified in study procedures and instructions provided to the subject. Subject or caregivers will be instructed to subcutaneously administer adalimumab or PTM adalimumab study medication once every other week according to the instructions provided to them. On weeks when study visits are scheduled, the injection should be planned to occur as outlined in the Priority of Assessments (Section 6.6.1).

At the investigational site, all adalimumab supplies and PTM adalimumab must be handled and stored safely and properly, and kept in a secured location to which only the investigator and authorized staff have access.

5.4. Prior and Concomitant Medications

Concomitant therapies for treatment of pre-existing conditions may be continued during the study provided they are in accordance with the inclusion and exclusion criteria (Section 4), and the permitted and prohibited concomitant medication instructions throughout Section 5.4. These medications should be continued without variation of dose or regimen during the study, as much as possible.

All non-PsA medication(s) used within 30 days of consent, including any changes, are to be documented in the eCRF. All prior medication(s) used in the treatment for PsA will be documented in the eCRF.

At each study visit, the site will capture any and all medications taken by the subject since the last visit or during the visit (as applicable). Concomitant medications include prescription medications, non-prescription medications, naturopathic therapies, dietary supplements, vitamins and minerals.

In case new non-prohibited therapies need to be administered during the study, the risk / benefit to the subject should be carefully assessed and consideration given to the timing of any necessary introduction of new medications.

5.4.1. Concomitant Medications: PsA Related

Permitted concomitant medications for PsA should be kept stable as much as possible throughout the study and include:

- NSAIDs, at a stable dose and regimen, through the Week 16 Visit, as much as possible. On the day of any study visit, NSAIDs should be held 12 hours before the visit until all scheduled assessments have been completed for that visit day.

- Analgesics, including opioids and other non-NSAID based therapies, at a stable dose and regimen, as much as possible. On the day of any study visit, analgesics should be held 12 hours before the visit until all scheduled assessments have been completed for that day.

- Oral prednisone ≤10 mg daily (or equivalent), at a stable dose and regimen, through the Week 16 Visit. If there is a need for the use of additional corticosteroids (oral, parenteral, inhaled or other) for the treatment of an AE, it should be discussed with the Gilead Medical Monitor or designee in advance, as much as possible, as well as the possible discontinuation of study drug and / or the subject from the study. The AE and medications administered will be documented in the eCRF. See Section 5.4.1.2 for additional guidance on special circumstances for corticosteroids.

- Topical therapies for psoriasis (e.g. topical corticosteroids, coal tar, salicylic acid, vitamin D analogs, retinoids, anthralin, topical calcineurin inhibitors such as tacrolimus) at a stable dose and regimen through the Week 16 Visit.

- csDMARDs (maximum of 2 can be taken together during the study):

  a) MTX oral or SC up to 25 mg / week (must include concomitant use of a folic acid supplementation as per local standard of care / investigator judgment). Dose should be stable through the Week 16 Visit.

     NOTE: MTX may not be combined with leflunomide.

  b) Leflunomide up to 20 mg once daily orally Dose should be stable through the Week 16 Visit.

     NOTE: Leflunomide may not be combined with MTX.

  c) Sulfasalazine up to 3 g daily orally. Dose should be stable through the Week 16 Visit.

  d) Hydroxychloroquine up to 400 mg daily or chloroquine up to 250 mg daily. Dose should be stable through the Week 16 Visit.

  e) Apremilast up to 30 mg twice daily orally. Dose should be stable through the Week 16 Visit.

Dose adjustments for management of toxicity of the above medications are allowed and should be documented, along with documentation of the AE which led to the change in the medication.

After the Week 16 Visit, subject's dose of concomitant medications for PsA can be reduced or tapered based on investigator judgement. The dose may be adjusted back up as needed, but should not exceed the stable dose identified on Day 1.

Please note that certain PsA concomitant medications such as antimalarial drugs, systemic corticosteroids, and NSAIDs, as well as certain non-PsA-related medications such as beta blockers, lithium, and ACE inhibitors, can cause dermatitis or exacerbate psoriasis.

5.4.1.1. PsA Rescue Therapy

Investigators should perform an ongoing assessment of a subject's need for rescue therapy beginning at the Week 16 Visit through the completion of the study. Sites will be assisted with this by receiving a one-time alert at the Week 16 Visit for subjects with <20% improvement from Day 1 in the TJC68 or SJC66 (these subjects are referred to as inadequate responders). At that time, it will be required to modify the subject's concomitant medication(s) by adjusting the dose of existing medication(s) and / or introducing new medication(s) based on investigator judgement along with consideration of the subject's medical history (e.g. comorbidities, history of concomitant medications, etc.). After the Week 16 Visit investigators will not receive an alert for subjects with <20% improvement; however, clinical judgement should be used to decide if the subject is not clinically improving and requires rescue therapy. The following medications are recommended as rescue therapy options to add or modify after Week 16: NSAIDs, opiate analgesics, csDMARDs, corticosteroids, and bioDMARDs. Subjects must discontinue study at time of bioDMARD initiation.

Starting at the Week 24 Visit, subjects who have <10% improvement from Day 1 in the TJC68 or SJC66 at two consecutive visits despite stable background PsA therapy should discontinue both study drug and study and adjust any PsA treatment as deemed appropriate by the investigator. Sites will be assisted with this by receiving a discontinuation of study alert when subjects reach this threshold at any time from the Week 24 Visit through the end of the study.

In cases where a subject has had recent modification of PsA therapy requiring time for further assessment, the investigator should use clinical judgement to decide if subjects should continue study drug and study despite receiving the discontinuation alert.

Subjects who discontinue study drug at any point during the LTE should also exit the study.

5.4.1.2. Special Circumstances for Corticosteroids, Hyaluronate Therapy, and Biologics

At any time during the study if there is a need for the use of additional corticosteroids (oral, parenteral, inhaled or other) for the treatment of an AE (e.g. asthma exacerbation, allergy, or anaphylaxis reaction, etc.), it should be discussed with the Gilead Medical Monitor or its designee in advance, as much as possible, as well as the possible discontinuation of study drug and / or the study. The AE and medications administered will be documented in the eCRF.

During the LTE subjects may receive intra-articular corticosteroids or hyaluronate therapy for treatment of PsA if needed. The dose of corticosteroid injected should not exceed the equivalent dose of triamcinolone 80 mg suspension. For the analysis of the SJC66 and TJC68, these joints will be considered "not assessable" for 3 months from the time of the intra-articular injection and should be documented.

Concomitant biologics not given for the treatment of an inflammatory arthropathy (i.e. given for osteoporosis) may be allowable after written approval from the Gilead Medical Monitor or designee.

5.4.2. Concomitant Medications: Non-PsA Related

Non-PsA related therapy such as hormone replacement therapy, thyroid replacement, and other chronic therapies (such as those for well-controlled diabetes or hypertension) are permitted during the study, and should be kept at a stable dose and regimen, as much as possible.

Vitamin, mineral, or herbal supplementations are permitted during the study per judgment of investigator, and should be kept at a stable dose and regimen, as much as possible.

Female subjects of childbearing potential must agree to use highly effective birth-control methods as outlined in Appendix 3. The use of contraceptives will be recorded in the Concomitant Therapy section of the eCRF. Applicable procedures and treatment guidance based on package inserts will be followed.

5.4.3. Prohibited Concomitant Medications

Prohibited concomitant medications at the time of randomization, with applicable washout periods, are included in the Exclusion Criteria (Section 4.3).

Prohibited concomitant medications during the course of the study are as follows:

- Throughout the entire study unless required for rescue therapy after the Week 16 Visit:
  - Intra-articular or parenteral corticosteroids
  - Intra-articular hyaluronate injections
  - Small molecule immunomodulators that were not already started at the time of study enrollment (i.e. subject cannot start methotrexate, hydroxychloroquine, etc., as a new concomitant medication after Day 1unless required for rescue therapy after the Week 16 Visit)
  - Ultraviolet light therapy
  - BioDMARDs (e.g. etanercept, golimumab, abatacept, secukinumab, etc.) If required for rescue therapy per investigator judgment, subjects must discontinue study at time of bioDMARD initiation.
  - B-cell depleting agents (e.g. rituximab, etc.) If required for rescue therapy per investigator judgment, subjects must discontinue study at time of B-cell depleting agent initiation.

- Throughout the entire study:
  - JAK inhibitors (e.g. tofacitinib, baricitinib, etc.)
  - Potent Pg-p inducers (e.g. rifampin, phenytoin, carbamazepine, and St. John's wort)
  - Oral or injectable gold
  - D penicillamine
  - Any cytotoxic agent, including chlorambucil, cyclophosphamide, nitrogen mustard, and other alkylating agents
  - Investigational drugs or devices

5.4.4. Vaccine Guidelines

Prior to study participation, it is recommended that the subject's vaccinations be brought up to date according to local vaccination standards. The varicella vaccine is of particular importance for immunocompromised patients.

Live or attenuated vaccines (including, but not limited to varicella and inhaled flu vaccine) are prohibited ≤30 days of the Day 1 Visit, throughout the study, and for 4 weeks after the last dose of study drug.

Subjects should be advised to avoid routine household contact with persons vaccinated with live / attenuated vaccine components. A study subject's exposure to household contacts should be avoided for the below stated time periods:

- Varicella or attenuated typhoid fever vaccination – avoid contact for 4 weeks following vaccination
- Oral polio vaccination – avoid contact for 6 weeks following vaccination
- Attenuated rotavirus vaccine – avoid contact for 10 days following vaccination
- Inhaled flu vaccine – avoid contact for 1 week following vaccination

Inactivated vaccines (such as inactivated flu vaccines) should be administered according to local vaccination standards whenever medically appropriate; however, there are no available data on the concurrent use of filgotinib and its impact on immune responses following vaccination.

5.5. Accountability for Study Drugs

The investigator is responsible for ensuring adequate accountability of all used and unused study drugs. This includes acknowledgement of receipt of each shipment of study drugs (quantity and condition). All used and unused study drugs dispensed to subjects must be returned to the site.

Filgotinib, adalimumab, and PTMs accountability records will be provided to each study site to:

- Record the date received and quantity of study drugs
- Record the date, subject number, subject initials, the study drug number dispensed
- Record the date, quantity of used and unused study drugs returned, along with the initials of the person recording the information
- Dispensing records will include the initials of the person dispensing the study drug or supplies

5.5.1. Study Drug Return or Disposal

At study initiation, the monitor will evaluate the site's standard operating procedure for study drug disposal / destruction in order to ensure that it complies with Gilead's requirements. Study drug may be returned or destroyed on an ongoing basis during the study, if appropriate. At the end of the study, following final drug inventory reconciliation by the monitor, the study site will dispose of and / or destroy all unused study drug supplies, including empty containers, according to these procedures. If the site cannot meet Gilead's requirements for disposal, arrangements will be made between the site and Gilead or designee for destruction or return of unused study drug supplies.

All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

For additional information about study drug accountability and return, refer to Section 9.1.8

6. STUDY PROCEDURES

The study procedures to be conducted for each subject enrolled in the study are presented in tabular form in Appendix 2. Assessments that need specific attention are described in the text that follows.

The investigator must document any deviation from protocol procedures and notify the Sponsor or designee.

6.1. Part 1 – Main Study (Screening through Week 16 Visit)

6.1.1. Screening Visit

Entry into screening does not guarantee enrollment into the study. In order to manage the total trial enrollment, Gilead, at its sole discretion, may suspend screening and / or enrollment at any site or trial-wide at any time.

Subjects will be screened ≤28 days before randomization to determine eligibility for participation in the study. Study assessments will be completed as specified in the Study Procedures Table (Appendix 2). Prior to any assessments being performed, a written consent must be obtained.

Subjects meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic ≤28 days after screening for randomization into the study.

6.1.1.1. MRI Investigation

Subjects meeting all of the Main Study inclusion criteria and none of the Main Study exclusion criteria may be entered into an MRI investigation if all MRI inclusion and none of the MRI exclusion criteria are met.

Subjects participating in the MRI investigation must have an acceptable baseline MRI as per the central review. Subject's MRIs should only be taken after all other eligibility criteria within the main study have been met. To allow for scheduling and reading of images, the screening period may be extended to 42 days, in these cases only. A single repeat MRI may be done if determined required by central review and must be completed before the Day 1 Visit. See Section 4.5 for additional information on MRI screen failures.

6.1.2. Day 1 Visit

Study assessments will be completed as specified in the Study Procedures Table (Appendix 2). At the end of the visit, subjects will be randomized. Refer to Appendix 7 for how days of treatment are numbered.

Subjects will be randomly allocated to a dosing group according to a pre-specified randomization scheme prepared by an independent statistician. Once confirmed eligible for the study, subjects will be randomized using a computerized IXRS system. Randomization will be stratified by geographic region, concurrent use of csDMARDs and / or apremilast at randomization (yes or no).

For each subject at each visit, the clinic will contact the IXRS system and for the appropriate kit number to be dispensed. The kit will contain the relevant study drugs for the period until the next dispensation visit.

Female subjects of child bearing potential will be provided at-home pregnancy tests for use at the Safety Follow-up Visit or as needed.

6.1.3. Week 2 Visit through Week 16 Visit

Study assessments will be completed as specified in the Study Procedures Table (Appendix 2).

For the first 16 weeks of study participation, subjects who temporarily interrupt or permanently discontinue blinded study drug for any reason are to continue with study visits and assessments through the Week 16 Visit, unless the subject withdraws consent, is lost to follow-up, and / or continuation in the study is medically contraindicated, per investigator's judgment. The Week 16 Visit will be their last in-clinic visit.

6.2. Part 2 - LTE (After the Week 16 Visit and up to 2 years)

After completion of the Main Study, subjects who have not permanently discontinued study drug will continue on to the LTE as follows:

Those who were assigned to the filgotinib groups will continue on the same study drug assignments.

Those who were assigned to the placebo or active comparator groups will be reassigned 1:1 in a blinded fashion to filgotinib 100 mg or 200 mg once daily.

Study assessments will be completed as specified in the Study Procedures Table (Appendix 2).

6.3. Early Termination (ET) Visit

If a subject discontinues the study early either during the Main Study or during the LTE, every attempt should be made to perform the required study-related ET procedures and Safety Follow-up Visit procedures as specified in the Study Procedures Table (Appendix 2).

6.3.1. Main Study Early Termination Visit

Subjects who permanently discontinue study drug prior to or at the Week 16 Visit and exit the study at the Week 16 Visit will need to perform a Main Study ET Visit in lieu of the Week 16 Visit. Subjects who permanently discontinue study drug and permanently discontinue study prior to the Week 16 Visit should perform a Main Study ET Visit ≤7 days of study discontinuation.

6.3.2. LTE Early Termination Visit

Subjects who permanently discontinue study drug during the LTE should perform an LTE ET Visit ≤7 days of study drug discontinuation.

6.4. Completion Visit

At the Week 120 Visit (~2.25 years), subjects will have their last in-clinic visit and will complete study assessments as specified in the Study Procedures Table (Appendix 2).

6.5. Safety Follow-up Visit

The Safety Follow-up Visit will be performed approximately 4 weeks after a subject's last in-clinic visit in either the Main Study or the LTE as specified in the Study Procedures Table (Appendix 2). This visit should be done by phone call unless otherwise required by region.

Subjects in Europe will have additional Safety Follow-up Visits. These visits will occur 8, 12, and 16 weeks after their last SC injection of study drug and should also be done by phone call unless otherwise required by region. If the subject's last study visit is greater than or equal to 16 weeks from their last SC injection, the additional Safety Follow-up Visits will not be required.

6.6. Study Assessments

Study Assessments will be performed at the time points indicated in the Study Procedures Table (Appendix 2).

6.6.1. Assessment Order

The recommended order of study procedures is as follows:

1) Patient Reported Outcomes (PROs)

   NOTE: It is recommended that the PROs are performed at the beginning of each visit prior to any other visit-related procedures, other than signing of informed consent.

2) Clinical assessments (e.g. physical exam, physician reported outcome measures, recording of history, AEs, concomitant medications, etc.)

3) Laboratory sample collection, imaging and biopsy assessments, as applicable

4) Study drug dosing

6.6.2. Demographics, Medical History, and Physical Exams

At the Screening Visit, subject's demographics (year of birth, age, sex, race, ethnicity, etc.), baseline disease characteristics (current medical conditions, spondylitis, history of extra-articular involvement such as uveitis, psoriasis, inflammatory bowel disease (IBD), dactylitis, enthesitis, etc.), PsA diagnosis, prior PsA treatment(s) and medical history will be collected. This will include but is not limited smoking status, average weekly alcohol consumption, any other chronic medical conditions, and prior surgeries.

Complete physical examinations and symptom-driven physical examinations will be performed at the time points indicated in the Study Procedures Table (Appendix 2). A complete physical examination should include source documentation of general appearance, and the following body systems: Head, neck and thyroid; eyes, ears, nose, throat, mouth and tongue; chest (excluding breasts); respiratory; cardiovascular; lymph nodes; abdomen; skin, hair, nails; musculoskeletal; and neurological. Any changes from Baseline will be recorded. Height will be measured at the Screening Visit only.

6.6.3. Efficacy

6.6.3.1. Patient Reported Outcomes

Comprehensive descriptions and instructions for each PRO are provided in the electronic clinical outcomes assessments materials. Examples can be found in Appendix 9. - Appendix 26.

PROs collected in this study will include:

- HAQ-DI: Health Assessment Questionnaire – Disability Index
- FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy – Fatigue Scale
- SF-36v2: 36 - item Short - Form Health Survey Version 2
- PsAID-12: 12-item Psoriatic Arthritis Impact of Disease
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- PGADA: Patient's Global Assessment of Disease Activity
- PGAPI: Patient's Global Assessment of Psoriatic Arthritis Pain Intensity

6.6.3.2. Clinical Reported Outcome Measurements

Comprehensive descriptions and instructions for each clinical assessment are provided in the electronic clinical outcomes assessments materials. Examples can be found in Appendix 9. - Appendix 26

Physician (or site staff designee) reported outcome measurements collected in this study include:

- PASI including BSA: Psoriasis Area and Severity Index including Body Surface Area
- mNAPSI: Modified Nail Psoriasis Severity Index
- PhGAP: Physician's Global Assessment of Psoriasis
- SPARCC Enthesitis Index and LEI: Spondyloarthritis Research Consortium of Canada Enthesitis Index and Leeds Enthesitis Index
- SJC66 / TJC68: Swollen and Tender Joint Count
- LDI: Leeds Dactylitis Index
- PhGADA: Physician's Global Assessment of Disease Activity

6.6.3.3. Independent Assessor

Assessment of tender and swollen joints, dactylitis, enthesitis, and psoriasis of the skin and nails will take place at the time points indicated in the Study Procedures Table (Appendix 2). The clinical assessment forms are provided in Appendix 20, Appendix 21, Appendix 23, Appendix 24, and Appendix 25.

An independent clinical assessor with adequate training including completion of the required training provided by the Sponsor, and experience in performing these assessments will be designated at each study site to perform all relevant assessments including SJC66 / TJC68, SPARCC Enthesitis Index and LEI, LDI, PASI including BSA, and mNAPSI should be blinded to the other study assessments performed on that day. The assessor should preferably be a rheumatologist; however, if a rheumatologist is not available, it should be a health care worker who has completed the required training provided by the Sponsor and has experience in performing these assessments. The assessor should remain the same throughout the study per subject, as much as possible. It is required that the designated assessor identify an appropriate back up assessor to provide coverage if the designated assessor is absent.

6.6.4. Safety Assessments

6.6.4.1. Vital Signs and Weight

Vital signs and weight will be performed at the time points indicated in the Study Procedures Table (Appendix 2).

Vital signs should be taken after the subject has been resting for 5 minutes and will include heart rate, respiratory rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), and body temperature. Weight will be measured without shoes.

6.6.4.2. 12-lead Electrocardiogram

A resting 12-lead ECG will be performed at the Screening Visit only.

The ECG should be obtained after the subject has been resting in the supine position for 5 min and will include heart rate (HR), QRS, uncorrected QT, morphology, and rhythm analysis. ECGs will be interpreted by the investigator (or qualified designee) for clinical significance and results will be entered into the eCRF.

6.6.4.3. Pregnancy Test

For females of childbearing potential only, pregnancy tests will be performed at the time points indicated in the Study Procedures Table (Appendix 2).

For eligibility, a serum pregnancy test will be performed at the Screening Visit and a urine pregnancy test will be performed at the Day 1 Visit. Urine pregnancy tests will be performed at all other visits. Subjects will be provided an at-home pregnancy test for use during the LTE, at the Safety Follow-up Visit, or as needed. Per local regulation LTE and Safety Follow-up Visit Pregnancy tests may be performed in-clinic.

The site will call the subject every 4 weeks during the LTE or at the Safety Follow-up Visit, if there is not a clinic visit scheduled, in order to obtain results. Results will be recorded in the source documents and eCRF. If any pregnancy test is positive, study drug should be immediately interrupted and the subject should present to the site for further evaluation and testing, including a serum pregnancy test.

6.6.5. Laboratory Assessments

The hematology, serum chemistry, and urinalysis will be performed at a central laboratory. CCI [redacted]. A list of scheduled laboratory tests for this study is available in Appendix 5. Reference ranges will be supplied by the central laboratory and will be used by the investigator to assess the laboratory data for clinical significance and pathological changes.

Blood samples will be collected by venipuncture CCI [redacted] at the time points indicated in the Study Procedures Table (Appendix 2). In addition, urine samples for the clinical laboratory assessments will be collected. Fasting (no food or drinks, except water) of at least 8 hours will be required prior to collection of blood samples for lipid testing only.

Laboratory values outside the normal range will be flagged and clinical relevance will be assessed by the investigator. Following up on laboratory abnormalities is the responsibility of the investigator. More frequent sampling as well as additional tests may be performed as deemed necessary by the investigator.

NOTE: In the case where clinically significant laboratory test results are a potential reason for discontinuation from the study drug, retesting of the affected parameter(s) should be prompt (≤7 days) after the investigator has consulted with the Gilead Medical Monitor or designee. A decision regarding subject discontinuation from study drug should be made after the results from the retest are available.

The details of sample handling and shipment instructions will be provided in a separate laboratory manual.

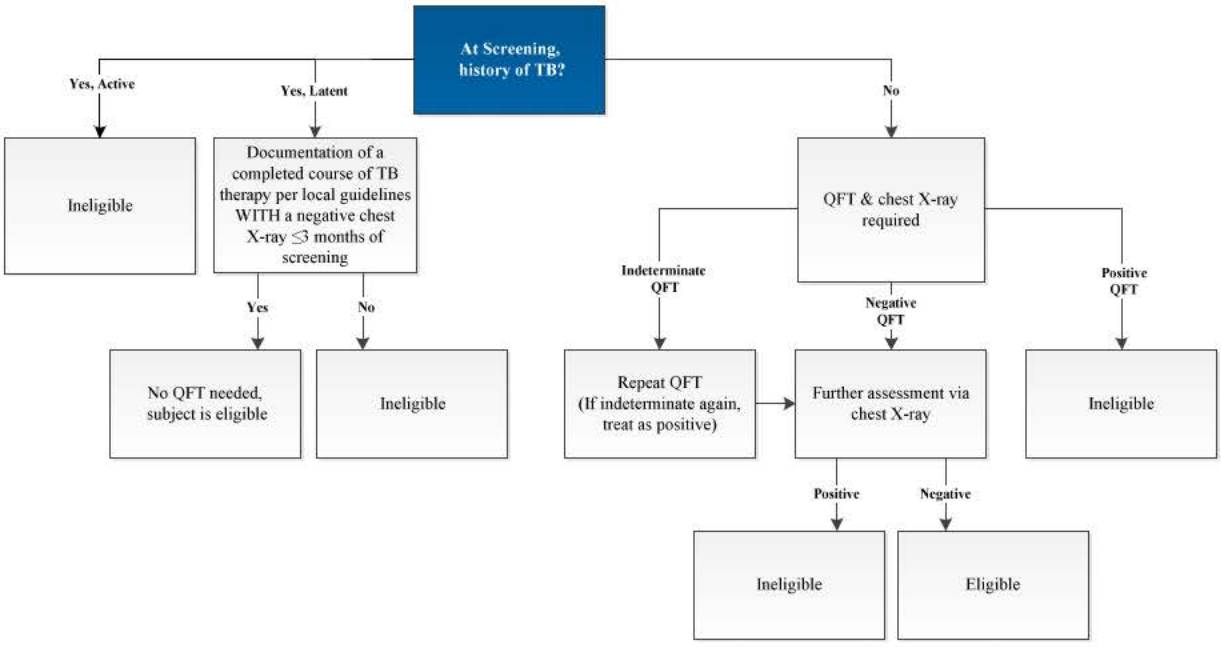
6.6.5.1. Tuberculosis Testing

Testing will be performed as a combination of a QuantiFERON® TB-Gold Plus (QFT) central laboratory test AND a chest X-ray at the time points indicated in the Study Procedures Table (Appendix 2). Assessment of active or latent TB may be determined when both the QFT and X-ray results are available. Local laboratory tests are not allowed.

Screening TB Testing

Tuberculosis testing will be performed at the Screening Visit as outlined below:

Figure 6-1. Tuberculosis Testing at the Screening Visit



If subjects have active TB, defined as a positive QFT and / or positive chest X-ray, they will not be permitted to enroll in the study, per Section 4.2.

Subjects with a history of latent TB, defined as a positive QFT and negative chest X-ray, must have documentation of a completed course of therapy, as per local standard of care, WITH a negative chest X-ray ≤3 months of the Screening Visit. In these cases, no QFT should be performed. Subjects who have a history of latent TB with no documentation of a completed course of therapy will be ineligible to enroll, per Section 4.2. Subjects with latent TB can be screened for this study if they complete a course of latent TB therapy.

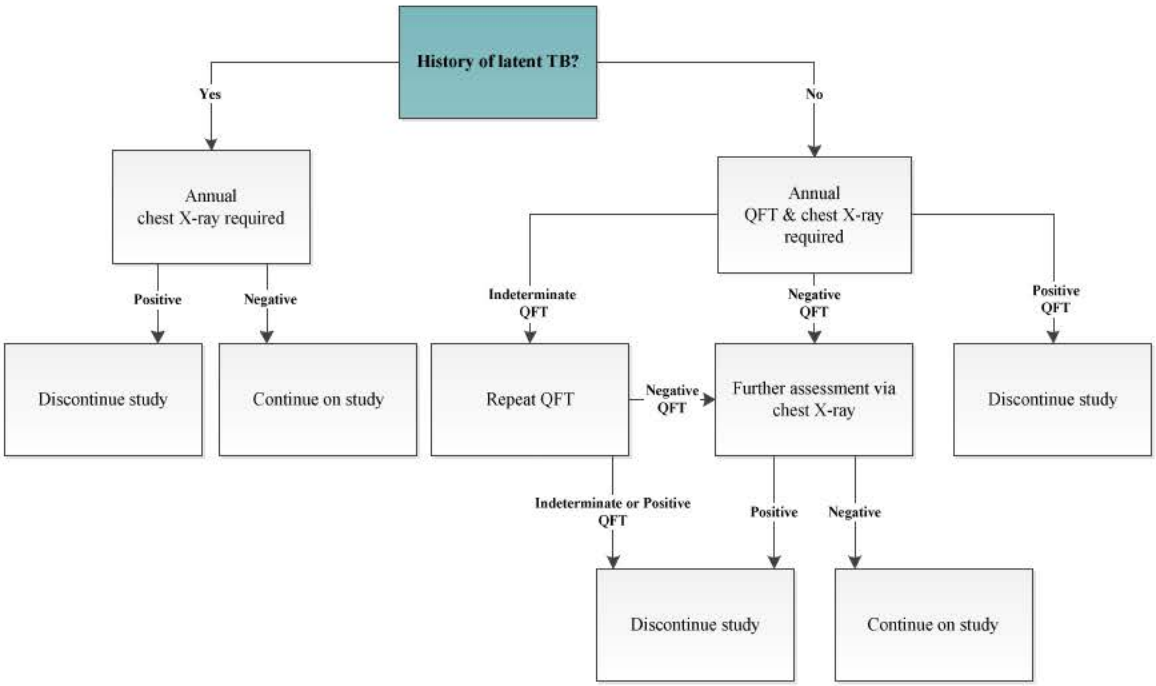
Subjects with positive QFT results from the central laboratory may not repeat QFTs in a local or the central laboratory; subjects must screen fail and should be treated per local standard.

Subjects with indeterminate QFT results may repeat the QFT only once through the central laboratory. If the repeat result is also indeterminate, the result will be considered positive for the purposes of this study and subjects should be evaluated for active TB via a chest X-ray. If the chest X-ray is negative the subject will be allowed to enter the study only after completion of latent TB therapy per local guidelines and provide appropriate documentation. If the chest X-ray is positive the subject will not be allowed to enter the study and should seek medical attention per local guidelines. QFT tests with indeterminate results can be repeated only once.

LTE TB Testing

Tuberculosis testing will be performed during the LTE as outlined below:

Figure 6-2. Tuberculosis Testing During the LTE



Subjects with a history of latent TB will be monitored annually with a chest X-ray. No QFT should be performed as indicated in Appendix 2.

Subjects without a history of TB will be monitored with an annual QFT and chest X-ray

- For subjects with negative QFT results, a chest X-ray is required
- For subjects with newly positive (converted) QFT results, subjects must **immediately** discontinue study drug, discontinue study and be evaluated for active TB. A positive initial test cannot be followed by a repeat test.
- For subjects with indeterminate QFT results, subjects must **immediately** interrupt study drug, and repeat the QFT via central laboratory with an Unscheduled Visit (in <2 weeks from the visit) and be evaluated for active TB. If the repeat result is also indeterminate, the result will be considered positive for the purposes of this study and subjects should discontinue study and be evaluated for active TB. QFT tests with indeterminate results can be repeated only once.

6.6.5.2. Viral Monitoring

Subjects who test positive for chronic HBV or HCV at Screening will be monitored as outlined in the Study Procedures Table (Appendix 2).

6.6.6. Imaging Assessments

6.6.6.1. MRI

MRIs will be performed at site when and where available. MRIs will be taken on one hand / wrist prior to the first dose of study drug and repeated at the Week 16 Visit. Assessment will be on the same hand / wrist throughout the study. MRIs will be scored by central read as outlined in the imaging manual.

CCI [redacted]

CCI [redacted]

[redacted]

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of Adverse Events, Adverse Reactions, and Serious Adverse Events

7.1.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical study subject administered a medicinal product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and / or unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs may also include pre- or post-treatment complications that occur as a result of protocol specified procedures, lack of efficacy, overdose, drug abuse / misuse reports, or occupational exposure. Pre-existing events that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an adverse event and must be reported
- Pre-existing diseases, conditions, or laboratory abnormalities present or detected before the Screening Visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (e.g. hospitalization for elective surgery, social and / or convenience admissions)
- Overdose without clinical sequelae (see Section 7.7.1)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history eCRF.

7.1.2. Serious Adverse Events

A **serious adverse event** (SAE) is defined as an event that, at any dose, results in the following:

- Death
- Life-threatening (NOTE: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)

- In-patient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability / incapacity
- A congenital anomaly / birth defect
- A medically important event or reaction: such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is a reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse. For the avoidance of doubt, infections resulting from contaminated medicinal product will be considered a medically important event and subject to expedited reporting requirements.

7.1.3. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities without clinical significance are not recorded as AEs or SAEs. However, laboratory abnormalities (e.g. clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to study drug interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (e.g. electrocardiogram, X-rays, vital signs) that are associated with signs and / or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (e.g. anemia), not the laboratory result (i.e. decreased hemoglobin).

For specific information on handling of clinical laboratory abnormalities in this study, please refer to Section 7.5.

7.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified subinvestigator is responsible for assessing AEs and SAEs for causality and severity, and for final review and confirmation of accuracy of event information and assessments.

7.2.1. Assessment of Causality for Study Drugs and Procedures

The investigator or qualified subinvestigator is responsible for assessing the relationship to study drug therapy using clinical judgment and the following considerations:

- **No**: Evidence exists that the AE has an etiology other than the study drug. For SAEs, an alternative causality must be provided (e.g. pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).
- **Yes**: There is reasonable possibility that the event may have been caused by the investigational medicinal product.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of AE reporting.

The relationship to study procedures (e.g. invasive procedures such as venipuncture or biopsy) should be assessed using the following considerations:

- **No:** Evidence exists that the adverse event has an etiology other than the study procedure.
- **Yes:** The adverse event occurred as a result of protocol procedures, (e.g. venipuncture).

7.2.2. Assessment of Severity

The severity of AEs will be graded using the modified Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. For each episode, the highest grade attained should be reported.

If a CTCAE criterion does not exist, the investigator should use the grade or adjectives: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening) or Grade 5 (fatal/death) to describe the maximum intensity of the adverse event. For purposes of consistency with the CTCAE, these intensity grades are defined in Table 7-1 below.

Table 7-1. Grading of Adverse Event Severity

Grade	Adjective	Description
Grade 1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate	Local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*
Grade 3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**
Grade 4	Life-threatening	Urgent intervention indicated
Grade 5	Fatal/Death	Fatal/Death related AE

* Activities of Daily Living (ADL) Instrumental ADL refer to opening preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

The only modification to the CTCAE criteria is the addition of a Grade 1 upper respiratory infection outlined in Table 7-2 below.

NOTE: Upper respiratory infection is defined as a disorder characterized by an infectious process involving the upper respiratory tract (nose, paranasal sinuses, pharynx, larynx, or trachea).

Table 7-2 Grading of Upper Respiratory Infection Severity

Grade	Adjective	Description
Grade 1	Mild	Mild symptoms; symptomatic relief (e.g. cough suppressant, decongestant)
Grade 2	Moderate	Moderate symptoms; oral intervention indicated (e.g. antibiotic, antifungal, antiviral)
Grade 3	Severe	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated
Grade 4	Life-threatening	Life-threatening consequences; urgent intervention indicated
Grade 5	Fatal/Death	Fatal/Death

7.3. Investigator Requirements and Instructions for Reporting Adverse Events and Serious Adverse Events to Gilead

Requirements for collection prior to study drug initiation:

After informed consent, but prior to initiation of study medication, the following types of events should be reported on the eCRF: all SAEs and AEs related to protocol-mandated procedures.

Adverse Events

Following initiation of study medication, collect all AEs, regardless of cause or relationship, throughout the duration of the study, including at the protocol-required Safety Follow-up Visit must be reported to the eCRF database as instructed.

All AEs should be followed up until resolution or until the AE is stable, if possible.
Gilead Sciences may request that certain AEs be followed beyond the protocol defined follow-up period.

Serious Adverse Events

All SAEs, regardless of cause or relationship, that occurs after the subject first consents to participate in the study (i.e. signing the informed consent) and throughout the duration of the study, including 30 days after last in clinic visit, must be reported to the eCRF database and Gilead PVE, as instructed. This also includes any SAEs resulting from protocol-associated procedures performed after informed consent is signed.

Investigators are not obligated to actively seek SAEs after the protocol defined follow-up period; However, if the investigator learns of any SAEs that occur after study participation has concluded and the event is deemed relevant to the use of study drug, he / she should promptly document and report the event to Gilead PVE.

- All AEs and SAEs will be recorded in the eCRF database within the timelines outlined in the eCRF completion guideline.

Electronic Serious Adverse Event (eSAE) Reporting Process

- Site personnel record all SAE data in the eCRF database and from there transmit the SAE information to Gilead PVE ≤24 hours of the investigator's knowledge of the event. Detailed instructions can be found in the eCRF completion guidelines.
- If for any reason it is not possible to record the SAE information electronically, i.e. the eCRF database is not functioning, record the SAE on the paper serious adverse event reporting form and submit ≤24 hours to:

  Gilead PVE: Fax: PPD
  E-mail: PPD

- As soon as it is possible to do so, any SAE reported via paper must be transcribed into the eCRF Database according to instructions in the eCRF completion guidelines.
- If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary.
- All AEs and SAEs will be recorded in the eCRF database within the timelines outlined in the eCRF completion guideline.
- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be submitted by e-mail or fax when requested and applicable. Transmission of such documents should occur without personal subject identification, maintaining the traceability of a document to the subject identifiers.
- Additional information may be requested to ensure the timely completion of accurate safety reports.
- Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's eCRF and the event description section of the SAE form.

7.4. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the EU Clinical Trials Directive (2001 / 20 / EC) and relevant updates, and other country-specific legislation or regulations, Gilead may be required to expedite to worldwide regulatory agencies reports of SAEs, serious adverse drug reactions (SADRs), or SUSARs. In accordance with the EU Clinical Trials Directive (2001 / 20 / EC), Gilead or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable SUSARs as outlined in current regulations.

Assessment of expectedness for SAEs will be determined by Gilead using reference safety information specified in the investigator's brochure. Assessment of expectedness for adalimumab SAEs will be determined by the adalimumab EU SmPC (SmPC Section 4.8) or relevant local label as applicable.

All investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any study drug. The investigator should notify the IRB / IEC of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

7.5. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities are usually not recorded as AEs or SAEs. However, laboratory abnormalities (e.g. clinical chemistry, hematology, and urinalysis) independent of the underlying medical condition that require medical or surgical intervention or lead to investigational medicinal product interruption or discontinuation must be recorded as an AE or SAE, as applicable. In addition, laboratory or other abnormal assessments (e.g. ECG, X-rays, vital signs) that are associated with signs and / or symptoms must be recorded as an AE or SAE if they meet the definition of an AE (or SAE) as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (i.e. anemia) not the laboratory result (i.e. decreased hemoglobin).

Adverse events will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA). Severity should be recorded and graded according to the CTCAE Version 5.0, which can be found at:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

All clinical and clinically significant laboratory toxicities will be managed according to uniform guidelines detailed in Appendix 4 and as outlined below.

7.5.1. Grades 1 and 2 Laboratory Abnormality or Clinical Event

- For study specific interruption and stopping criteria, please refer to Section 3.5 (Criteria for Interruption or Discontinuation of study treatment)

7.5.2. Grades 3 Laboratory Abnormality or Clinical Event

- For study specific interruption and stopping criteria, please refer to Section 3.5 (Criteria for Interruption or Discontinuation of study treatment)

- For Grades 3 Laboratory Abnormality or Clinical Event not specified in Section 3.5, the following toxicity management guidelines apply:

  — For Grade 3 clinically significant laboratory abnormality or clinical event, study drug may be continued if the event is considered to be unrelated to study drug.

  — For a Grade 3 clinical event, or clinically significant laboratory abnormality confirmed by repeat testing, that is considered to be related to study drug, investigational medicinal product should be withheld until the toxicity returns to ≤ Grade 2.

  — If a laboratory abnormality recurs to ≥ Grade 3 following re-challenge with study drug and is considered related to study drug, then study drug should be permanently discontinued and the subject managed according to local clinical practice. Recurrence of laboratory abnormalities considered unrelated to study drug may not require permanent discontinuation.

7.5.3. Grades 4 Laboratory Abnormality or Clinical Event

- For study specific interruption and stopping criteria, please refer to Section 3.5 (Criteria for Interruption or Discontinuation of study treatment)

- For Grade 4 Laboratory Abnormality or Clinical Event not specified in Section 3.5, the following toxicity management guidelines apply:

  — For a Grade 4 clinical event or clinically significant Grade 4 laboratory abnormality confirmed by repeat testing that is considered related to study drug, study drug should be permanently discontinued and the subject managed according to local clinical practice. The subject should be followed as clinically indicated until the laboratory abnormality returns to baseline or is otherwise explained, whichever occurs first. A clinically significant Grade 4 laboratory abnormality that is not confirmed by repeat testing should be managed according to the algorithm for the new toxicity grade.

- Study drug may be continued without dose interruption for a clinically non-significant Grade 4 laboratory abnormality (e.g. Grade 4 creatine kinase (CK) after strenuous exercise or triglyceride elevation that is non-fasting or that can be medically managed) or a clinical event considered unrelated to investigational medicinal product.

7.6. Toxicity Management

Treatment-emergent toxicities will be noted by the investigator and brought to the attention of the Gilead Sciences Medical Monitor or designee, who will have a discussion with the investigator and decide the appropriate course of action. Whether or not considered treatment-related, all subjects experiencing AEs must be monitored periodically until symptoms subside, any abnormal laboratory values have resolved or returned to baseline levels or they are considered irreversible, or until there is a satisfactory explanation for the changes observed.

Any questions regarding toxicity management should be directed to the Gilead Sciences Medical Monitor or designee.

7.6.1. Thromboembolic Events

Subjects experiencing a thromboembolic event should be evaluated for the overall risk of recurrent thromboembolism and referred to a specialist for further testing as appropriate (including but not limited to evaluation for an underlying inherited hypercoagulable state).

7.7. Special Situations Reports

7.7.1. Definitions of Special Situations

Special situation reports include all reports of medication error, abuse, misuse, overdose, occupational exposure, drug interactions, exposure via breastfeeding, unexpected benefit, transmission of infectious agents via the product, counterfeit or falsified medicine, and pregnancy regardless of an associated AE.

Medication error is any unintentional error in the prescribing, dispensing, preparation for administration or administration of an investigational product while the medication is in the control of a health care professional, patient, or consumer. Medication errors may be classified as a medication error without an AE, which includes situations of missed dose; medication error with an AE; intercepted medication error; or potential medication error.

Abuse is defined as persistent or sporadic intentional excessive use of an investigational product by a subject.

Misuse is defined as any intentional and inappropriate use of an investigational product that is not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as an accidental or intentional administration of a quantity of an investigational product given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labeling (as it applies to the daily dose of the subject in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s). Overdose cannot be established when the subject cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the subject has taken the additional dose(s).

Occupational exposure is defined as exposure to an investigational product as a result of one's professional or non-professional occupation.

Drug interaction is defined as any drug/drug, drug/food, or drug/device interaction.

Unexpected benefit is defined as an unintended therapeutic effect where the results are judged to be desirable and beneficial.

Transmission of infectious agents is defined as any suspected transmission of an infected agent through a GSI investigational product.

Counterfeit or falsified medicine is defined as any investigational product with a false representation of: a) its identity, b) its source, or c) its history.

7.7.2. Instructions for Reporting Special Situations

7.7.2.1. Instructions for Reporting Pregnancies

The investigator should report pregnancies in female study subjects that are identified after initiation of study medication and throughout the study, including the post study drug follow-up period, to Gilead PVE using the pregnancy report form within 24 hours of becoming aware of the pregnancy.

Refer to Section 7.3 and the eCRF completion guidelines for full instructions on the mechanism of pregnancy reporting.

The pregnancy itself is not considered an AE nor is an induced elective abortion to terminate a pregnancy without medical reasons.

Any premature termination of pregnancy (e.g. a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE. The underlying medical reason for this procedure should be recorded as the AE term.

A spontaneous abortion is always considered to be an SAE and will be reported as described in Sections 7.1.1 and 7.1.2. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead PVE.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to Gilead PVE using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead PVE. Gilead PVE contact information is as follows:
Email: PPD and Fax: PPD.

Pregnancies of female partners of male study subjects exposed to Gilead or other study drugs must also be reported and relevant information should be submitted to Gilead PVE using the pregnancy and pregnancy outcome forms within 24 hours. Monitoring of the subject should continue until the conclusion of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead PVE, fax number PPD or email PPD

Refer to Appendix 3 or Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.7.2.2. Reporting Other Special Situations

All other special situation reports must be reported on the special situations report form and forwarded to Gilead PVE within 24 hours of the investigator becoming aware of the situation. These reports must consist of situations that involve study drug (including adalimumab) and / or other Gilead medications.

Special situations involving non-Gilead medications do not need to be reported on the special situations report form; however, for special situations that result in AEs due to a non-Gilead medication(s), the AE should be reported on the AE form.

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as “misuse,” but may be more appropriately documented as a protocol deviation.

Refer to Section 7.3 and the eCRF completion guidelines for full instructions on the mechanism of special situations reporting.

All clinical sequelae in relation to these special situation reports will be reported as AEs or SAEs at the same time using the AE eCRF and / or the SAE report form. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

Analysis objectives are aligned with the objectives specified in Section 2.

8.1.2. Primary Endpoint

The primary endpoint is listed in Section 3.1.1.

The primary null hypotheses are listed in Appendix 6.

8.1.3. Secondary Endpoints

The key secondary endpoints, other secondary CCI [redacted] endpoints are listed in Sections 3.1.2 and 3.1.3.

The key secondary hypotheses are listed in Appendix 6.

8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. Efficacy

The primary analysis set for efficacy analyses will be the Full Analysis Set (FAS), which includes all randomized subjects who received at least one dose of study drug.

8.2.1.2. Safety

The primary analysis set for safety analyses will be the Safety Analysis Set, which includes all subjects who received at least one dose of study drug.

CCI [redacted]

[redacted] CCI

CCI [redacted]

[redacted]

8.3. Data Handling Conventions

Values for missing safety laboratory data will not be imputed. If no baseline laboratory value is available, the baseline value will be assumed to be normal (i.e. no grade [Grade 0]) for the summary of graded laboratory abnormalities. If the safety laboratory results for a subject are missing for any reason at a time point, the subject will be excluded from the calculation of summary statistics for that time point.

Laboratory data that are continuous in nature but are less than the lower limit of quantitation or above the upper limit of quantitation will be imputed to the value of the lower or upper limit minus or plus one significant digit, respectively (e.g. if the result of a continuous laboratory test is <20, a value of 19 will be assigned; if the result of a continuous laboratory test is <20.0, a value of 19.9 will be assigned).

8.4. Demographic Data and Baseline Characteristics

Demographic and baseline measurements will be summarized using standard descriptive methods – 8-number summary (n, mean, SD, median, Q1, Q3, minimum, maximum) for continuous variables and the number and percentage of subjects per category for categorical variables.

Demographic summaries will include sex, race, ethnicity, and age.

Baseline characteristics will include randomization stratification factors, serum CRP, joint counts, HAQ-DI, and other variables of interest.

8.5. Efficacy Analysis

All continuous efficacy endpoints will be summarized using 8-number summary (n, mean, SD, median, Q1, Q3, minimum, maximum) by treatment group. All categorical efficacy endpoints will be summarized with the number and percentage of subjects who meet the endpoint or category definition by treatment group.

Besides the efficacy analyses specified in the protocol, sensitivity analyses may be performed for the efficacy assessments. More details on efficacy analyses will be described in the SAP.

8.5.1. Primary Analysis

8.5.1.1. Primary Estimand

The primary estimand corresponding to the treatment policy strategy is defined by the 4 attributes below:

1) Population: subjects in the FAS.

2) Variable / endpoint: binary ACR20 response variable at Week 12 indicating if a subject meets the ACR20 response criteria at Week 12.

3) Accounting for intercurrent events: include all on-study data regardless of protocol violations, use of rescue medication, change in background medication, and study drug discontinuation.

4) Population-level summary: the treatment difference in the percentage of subjects meeting ACR20 response criteria between each filgotinib group and the placebo group.

8.5.1.2. Main Estimator

A logistic regression analysis with treatment groups and stratification factors in the model will be used to analyze the primary endpoint. For subjects who do not have sufficient measurements to establish efficacy at Week 12, their data will be imputed using multiple imputation assuming that missing data are missing at random (MAR).

Sensitivity analyses to evaluate the robustness of results to violations of any assumptions made regarding the data missingness mechanisms will be specified in the SAP.

8.5.2. Secondary Analyses

8.5.2.1. Estimand

The main estimand corresponding to the treatment policy strategy for the key secondary endpoints is defined with the same attributes as in the primary estimand except that the variable / endpoint and population-level summary are endpoint specific. The key secondary endpoints are listed in Section 3.1.2. For the binary endpoints, the population-level summary is the treatment difference in the percentage of subjects meeting specified criteria for response between each filgotinib group and the placebo group. For the continuous endpoints, the population-level summary is the mean treatment difference between each filgotinib group and the placebo group.

8.5.2.2. Estimator

8.5.2.2.1. Superiority Test

For a superiority test of each filgotinib group compared to the placebo group on a binary efficacy endpoint, a logistic regression analysis with treatment groups and stratification factors in the model will be used.

For a superiority test of each filgotinib group compared to the placebo group on a continuous efficacy endpoint that is longitudinally collected, a mixed-effect model repeated measures (MMRM) analysis with treatment groups and stratification factors as fixed effects and subjects as a random effect in the model will be used. The model may also include visit, treatment-by-visit interaction, and the continuous baseline value as fixed effects.

8.5.2.2.2. Non-inferiority Test

The non-inferiority hypothesis based on the response rate of ACR20 at Week 12 (Appendix 6) will be tested using the 3-arm design approach proposed by {Liu 2014}, which utilize the data collected from the placebo, filgotinib, and adalimumab groups. The traditional non-inferiority null hypothesis is H_0: $\pi_T - \pi_C \leq -\delta$ where: π_T is the response rate for the treatment group (i.e. filgotinib), $\pi_C$is the response rate for the active control group (i.e. adalimumab), and δ is the non-inferiority margin, where $\delta = (1 - \theta)(\pi_C - \pi_P)$ is usually estimated from historical data and $\pi_P$is the response rate for the placebo group. For the 3-arm design, the null hypothesis can be equivalently transformed to H_0:$\frac{\pi_T - \pi_P}{\pi_C - \pi_P} \leq \theta$. For this hypothesis testing, the response rates for the active control and placebo groups are estimated from the study data. A value of 0.5 is selected for θ, implying that the treatment is "at least as good as or non-inferior to" the active control {Koch 1999}.

8.5.3. Hypothesis Testing Strategy

The graphical approach to sequentially rejective multiple test procedures (Appendix 6 and Appendix 7) will be used to control a family wise type I error rate at 5% (i.e. α = 0.05).

Within each filgotinib dosing regimen, the primary hypothesis will be first tested at α/2. If the primary hypothesis is rejected, then the next secondary hypothesis in the same filgotinib dosing regimen will be tested at α/2. Testing of the hypotheses happens sequentially in the same filgotinib dosing regimen. Once all hypotheses within the same filgotinib dosing regimen are rejected, then the respective α/2 can be passed on to the other regimen's hypotheses, that is, all hypotheses in the other filgotinib dosing regimen will be tested at α level.

The order of the key secondary hypotheses will be specified in the SAP.

8.6. Safety Analysis

All safety analyses will be performed using the Safety Analysis Set. Safety will be evaluated by assessments of clinical laboratory tests, physical examinations, vital signs measurements at various time points during the study, and by the documentation of AEs.

Safety endpoints will be summarized with the number and percentage of subjects with events or abnormalities for categorical values or 8-number summary (n, mean, SD, median, Q1, Q3, minimum, maximum) for continuous data by treatment group.

Two safety estimands, treatment policy and while on treatment, will be applied for the safety analysis.

In the analysis for the treatment policy estimand, all the safety data collected in the study will be included in the analysis. For while on treatment estimand, all the safety data collected up to 30 days after the last dose date of study drug will be included in the analysis. More details on safety analyses will be described in the SAP.

8.6.1. Extent of Exposure

A subject's extent of exposure to study drug will be generated from the study drug administration page of the eCRF. Exposure data will be summarized by treatment group. The duration of exposure to study drug will be expressed as the number of weeks between the first and last dose dates of study drug, inclusive, regardless of temporary interruptions in study drug administration and summarized by treatment group.

8.6.2. Adverse Events

Clinical and laboratory AEs will be coded using the MedDRA. System Organ Class, High-Level Group Term (HLGT), High-Level Term (HLT), Preferred Term (PT), and Lower-Level Term (LLT) will be attached to the clinical database.

Treatment-Emergent Adverse Events (TEAEs) are:

- Any AEs with an onset date of on or after the study drug start date and no later than the "analysis end date," which is defined separately for treatment policy estimand and while on treatment estimand as follows:

  Treatment policy estimand: the latest date of either the last reported date in the study or 30 days after permanent discontinuation of study drug

  While on treatment estimand: 30 days after permanent discontinuation of study drug

  OR

- Any AEs leading to premature discontinuation of study drug.

Summaries (number and percentage of subjects) of TEAEs by System Organ Class and PT will be provided by treatment group. TEAEs will also be summarized by relationship to study drug and severity. In addition, TEAEs leading to premature discontinuation of study drug will be summarized and listed.

8.6.3. Laboratory Evaluations

Selected laboratory data will be summarized using only observed data. Data and change from Baseline at all scheduled time points will be summarized.

Graded laboratory abnormalities will be defined using the CTCAE version 5.0 grading scheme. The incidence of treatment-emergent graded laboratory abnormalities will be summarized by treatment group.

CCI [redacted]

[redacted] CCI

CCI [redacted]

[redacted]

8.9. Sample Size

Sample size is determined based on the non-inferiority test of each filgotinib group compared to the adalimumab group on the ACR20 response rate at Week 12. When assuming the ACR20 response rate being 52% and 60% for the adalimumab and each filgotinib group, and 38.6% for the placebo group, 244 subjects in each filgotinib group and placebo group, and 122 subjects in the adalimumab group are required to obtain 90% power at a two-sided 0.025 significance level to demonstrate that filgotinib group preserves more than 50% of the effect of adalimumab with respect to the ACR20 response rate at Week 12.

A sample size of 244 subjects in each filgotinib group and the placebo group will provide over 95% power to detect a difference in ACR20 response rate of 21.4% at Week 12 (38.6% and 60% for the placebo group and each filgotinib group, respectively) using a two-sided 0.025 significance level superiority test.

In summary, the total sample size will be approximately 854 subjects.

8.10. Data Monitoring Committee

An external multidisciplinary DMC will review the progress of the study and perform interim reviews of safety data and provide recommendation to Gilead whether the nature, frequency, and severity of AEs associated with study treatment warrant the early termination of the study in the best interests of the participants, whether the study should continue as planned, or the study should continue with modifications. The DMC may also provide recommendations as needed regarding study design.

If there is a recommendation from the DMC to stop the study early or other significant action due to a potential safety issue, the appropriate GSI Representative may be provided with the unblinded DMC closed session reports, as needed, to escalate to the appropriate safety committee (per GSI's signal management process) to make an informed decision. Unblinding of specific GSI personnel will be documented per the appropriate SOPs.

The DMC's specific activities will be defined by a mutually agreed charter, which will define the DMC's membership, conduct and meeting schedule.

While the DMC will be asked to advise Gilead regarding future conduct of the study, including possible early study termination, Gilead retains final decision-making authority on all aspects of the study.

8.11. Event Adjudication Committee for Major Adverse Cardiovascular Events and Thromboembolic Events

An independent adjudication committee governed by a charter will be set up to perform adjudication of potential major adverse cardiovascular events as well as thromboembolic events reported during the study. The adjudication of these events will be performed in a blinded fashion for the purposes of data analysis, and not for monitoring of subject safety.

Additional information regarding the logistics of adjudication will be described in the charter.

8.12. Week 16 Analysis

A Week 16 analysis is planned after all randomized subjects have completed their Week 16 Visit (or prematurely discontinued from the study prior to Week 16). The time point of the primary efficacy endpoint is Week 12. The time points of the key secondary efficacy endpoints are Week 12 and Week 16. Therefore, at the time of the Week 16 analysis, all the primary and key secondary endpoints / hypotheses can be evaluated.

8.13. Interim Analysis in LTE

Interim analyses in the LTE may be performed at the Sponsor's discretion.

A Week 48 Interim Analysis in LTE will be performed if deemed necessary per the Sponsor's discretion when all enrolled subjects have completed their Week 48 Visit (or prematurely discontinued from the study prior to Week 48).

No adjustment for multiplicity will be applied for interim analyses in LTE because all analyses will be mainly descriptive.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with ICH E6(R2) Good Clinical Practices and applicable laws and regulations.

9.1.2. Financial Disclosure

The investigator and subinvestigators will provide documentation of their financial interest or arrangements with Gilead, or proprietary interests in the investigational drug under study. This documentation must be provided prior to the investigator's (and any subinvestigator's) participation in the study. The investigator and subinvestigator agree to notify Gilead of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last subject completes the protocol-defined activities.

9.1.3. Institutional Review Board (IRB) / Independent Ethics Committee (IEC) Review and Approval

The investigator (or Sponsor as appropriate according to local regulations) will submit this protocol, informed consent form, and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) to an IRB / IEC. The investigator will not begin any study subject activities until approval from the IRB / IEC has been documented and provided as a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IRB / IEC any modifications made to the protocol or any accompanying material to be provided to the subject after initial IRB / IEC approval, with the exception of those necessary to reduce immediate risk to study subjects.

9.1.4. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The investigator must use the most current IRB / IEC-approved consent form for documenting written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by IRB / IEC or local requirements. The consent form will inform subjects about genomic testing and sample retention, and their right to receive clinically relevant genomic analysis results.

9.1.5. Confidentiality

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only an identification code and any other unique identifier(s) as allowed by local law (such as year of birth) will be recorded on any form or biological sample submitted to the Sponsor, IRB / IEC, or laboratory. Laboratory specimens must be labeled in such a way as to protect subject identity while allowing the results to be recorded to the proper subject. Refer to specific laboratory instructions. NOTE: The investigator must keep a screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the trial. Subject data will be processed in accordance with all applicable regulations.

The investigator agrees that all information received from Gilead, including but not limited to the investigator brochure, this protocol, eCRF, the study drug, and any other study information, remain the sole and exclusive property of Gilead during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

9.1.6. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following two categories: (1) investigator's study file, and (2) subject clinical source documents.

The investigator's study file will contain the protocol / amendments, eCRF and query forms, IRB / IEC and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data should include sequential notes containing at least the following information for each subject:

- Subject identification (name, date of birth, gender);
- Documentation that subject meets eligibility criteria, i.e. history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria);
- Documentation of the reason(s) a consented subject is not enrolled
- Participation in study (including study number);
- Study discussed and date of informed consent;

- Dates of all visits;
- Documentation that protocol specific procedures were performed;
- Results of efficacy parameters, as required by the protocol;
- Start and end date (including dose regimen) of study drug, including dates of dispensing and return;
- Record of all adverse events and other safety parameters (start and end date, and including causality and severity);
- Concomitant medication (including start and end date, dose if relevant; dose changes);
- Date of study completion and reason for early discontinuation, if it occurs.

All clinical study documents must be retained by the investigator until at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (i.e. United States, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, by local regulations, or by an agreement with Gilead. The investigator must notify Gilead before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, Gilead must be notified in advance.

If the investigator cannot provide for this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Gilead to store these records securely away from the site so that they can be returned sealed to the investigator in case of an inspection. When source documents are required for the continued care of the subject, appropriate copies should be made for storage away from the site.

9.1.7. Case Report Forms

For each subject consented, an eCRF will be completed by an authorized study staff member whose training for this function is documented according to study procedures. eCRF should be completed on the day of the subject visit to enable the Sponsor to perform central monitoring of safety data. The Eligibility Criteria eCRF should be completed only after all data related to eligibility have been received. Subsequent to data entry, a study monitor will perform source data verification within the Electronic Data Capture (EDC) system. Original entries as well as any changes to data fields will be stored in the audit trail of the system. Prior to database lock (or any interim time points as described in the clinical data management plan), the investigator will use his / her log in credentials to confirm that the forms have been reviewed, and that the entries accurately reflect the information in the source documents. The eCRF capture the data required

per the protocol schedule of events and procedures. System-generated or manual queries will be issued to the investigative site staff as data discrepancies are identified by the monitor or internal Gilead staff, who routinely review the data for completeness, correctness, and consistency. The site coordinator is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (e.g. data entry error). At the conclusion of the trial, Gilead will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.6.

9.1.8. Study Drug Accountability and Return

Where possible, study drug should be destroyed at the site. If the site has an appropriate SOP for drug destruction as determined by Gilead, the site may destroy used (empty or partially empty) and unused study drug supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for central files. If study drug is destroyed on site, the investigator must maintain accurate records for all study drug destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the study drug. Upon study completion, copies of the study drug accountability records must be filed at the site. Another copy will be returned to Gilead.

If the site does not have an appropriate SOP for drug destruction, used and unused study drug supplies are to be sent to the designated disposal facility for eventual destruction. The study monitor will provide instructions for return.

9.1.9. Inspections

The investigator will make available all source documents and other records for this trial to Gilead's appointed study monitors, to IRBs / IECs, or to regulatory authority or health authority inspectors.

9.1.10. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Gilead. The investigator must submit all protocol modifications to the IRB / IEC in accordance with local requirements and receive documented IRB / IEC approval before modifications can be implemented.

9.2.2. Study Report and Publications

A clinical study report (CSR) will be prepared and provided to regulatory agencies. Gilead will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). NOTE: An abbreviated report may be prepared in certain cases.

Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

- The results of the study in their entirety have been publicly disclosed by or with the consent of Gilead in an abstract, manuscript, or presentation form or the study has been completed at all study sites for at least 2 years.
- The investigator will submit to Gilead any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation.
- No such communication, presentation, or publication will include Gilead's confidential information (see Section 9.1.5).
- The investigator will comply with Gilead's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection, if deemed necessary.

9.3. Joint Investigator / Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol, e.g. attendance at Investigator's Meetings. If required under the applicable statutory and regulatory requirements, Gilead will capture and disclose to Federal and State agencies any expenses paid or reimbursed for such services, including any clinical trial payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

In accordance with regulations and guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the accuracy of the data recorded in the eCRF.

The monitor is responsible for routine review of the eCRF at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any subject records needed to verify the entries on the eCRF. The investigator agrees to cooperate with the monitor to ensure that any problems detected through any type of monitoring (central, onsite) are resolved.

9.3.3. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of Gilead may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the Gilead Medical Monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or Gilead access to records, facilities, and personnel for the effective conduct of any inspection or audit.

9.3.4. Study Discontinuation

Both the Sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory authority(ies), IRBs, and IECs. In terminating the study, Gilead and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

10. REFERENCES

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11. APPENDICES

Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.
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FOSTER CITY, CA 94404, USA

STUDY ACKNOWLEDGEMENT

PENGUIN 1: A Phase 3, Randomized, Double blind, Placebo and Adalimumab-controlled Study to Evaluate the Efficacy and Safety of Filgotinib in Subjects with Active Psoriatic Arthritis Who Are Naïve to Biologic DMARD Therapy

GS-US-431-4566, Amendment 2, 17 April 2020

This protocol has been approved by Gilead Sciences, Inc. The following signature documents this approval.

PPD

Name (Printed)
Author

PPD

Signature

04/20/2020

Date

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.
I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Gilead Sciences, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (Printed)

Signature

Date

Site Number

Appendix 2. Study Procedures Table

EVENT		Part 1: Main Study								
Visit (±window)		Screen (-28 days to 0)	Day 1	Weeks (±3 days) 2	4	8	12	16	ET (±7 days)	Safety Follow-up (±7 days) [a]
Screening Assessments	Informed consent	X								
	Inclusion / Exclusion Criteria	X	X [b]							
	Demographics, Baseline / Disease Characteristics, PsA Diagnosis and Prior PsA Treatment, Medical History	X								
	Complete Physical Examination	X								
	TB Screening and Chest X-ray	X								
Patient Reported Outcomes	HAQ-DI: Health Assessment Questionnaire – Disability Index		X	X	X	X	X	X	X	
	FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy – Fatigue Scale		X		X			X	X	
	SF-36v2: 36-item Short-Form Health Survey Version 2		X		X			X	X	
	PsAID-12: 12-item Psoriatic Arthritis Impact of Disease		X		X			X	X	
	CCI [redacted]									
	PGADA: Patient's Global Assessment of Disease Activity		X	X	X	X	X	X	X	
	PGAPI: Patient's Global Assessment of Psoriatic Arthritis Pain Intensity		X	X	X	X	X	X	X	

EVENT		Part 1: Main Study								
Visit (±window)		Screen (-28 days to 0)	Day 1	Weeks (±3 days) 2	4	8	12	16	ET (±7 days)	Safety Follow-up (±7 days) [a]
Physician Reported Outcomes	CASPAR: Classification Criteria for Psoriatic Arthritis	X								
	PASI including BSA: Psoriasis Area and Severity Index including Body Surface Area		X		X	X	X	X	X	
	mNAPSI: Modified Nail Psoriasis Severity Index		X		X	X	X	X	X	
	PhGAP: Physician's Global Assessment of Psoriasis		X	X	X	X	X	X	X	
	SPARCC Enthesitis Index and LEI: Spondyloarthritis Research Consortium of Canada Enthesitis Index and Leeds Enthesitis Index		X		X	X	X	X	X	
	SJC66 / TJC68: Swollen and Tender Joint Count	X	X	X	X	X	X	X	X	
	LDI: Leeds Dactylitis Index		X		X	X	X	X	X	
	PhGADA: Physician's Global Assessment of Disease Activity		X	X	X	X	X	X	X	
Safety	Vital Signs and Weight	X	X	X	X	X	X	X	X	
	Symptom-Driven Physical Examination		X	X	X	X	X	X	X	
	12-Lead ECG	X								
	Pregnancy Test [c]	X	X	X	X	X	X	X	X	X

EVENT		Part 1: Main Study								
				Weeks (±3 days)						
Visit (±window)		Screen (-28 days to 0)	Day 1	2	4	8	12	16	ET (±7 days)	Safety Follow-up (±7 days) [a]
Laboratory	Hematology and Chemistry	X	X	X	X	X	X	X	X	
	Urinalysis	X								
	Endocrine: FSH, TSH, and HbA1c [d]	X								
	Lipid profile (fasting)		X					X	X [e]	
	Serum CRP [f]		X	X	X	X	X	X	X	
	CCI									
	CCI									
	CCI									
	Biomarker Samples [f]		X	X	X		X	X		
	Viral Serology [j]	X								
	Viral Monitoring [k]						X		X [e]	
	CCI									
	CCI									
Imaging	MRI [l]	X [m]						X		
Adverse Events		X	X	X	X	X	X	X	X	X
Concomitant Medications		X	X	X	X	X	X	X	X	X
Study Drug(s) Dispensation			X	X [n]	X	X	X	X		
Self-injection (or caregiver) Training [o]			X							

a Subjects in Europe will have additional Safety Follow-up Visits. These visits will occur 8, 12, and 16 weeks after their last SC injection of study drug and should also be done by phone call unless otherwise required by region. If the subject's last study visit is greater than or equal to 16 weeks from their last SC injection, the additional Safety Follow-up Visits will not be required.
b Eligibility criteria check based on: (1) laboratory results from the Screening Visit, (2) SJC / TJC at Screening and Day 1, and (3) urine pregnancy test at Day 1 for female subjects of childbearing potential.
c For eligibility, a serum pregnancy test will be performed at the Screening Visit and a urine pregnancy test will be performed at the Day 1 Visit. Urine pregnancy tests will be performed at all other visits. Subjects will be provided at home pregnancy tests for use during the LTE, at the Safety Follow-up Visit, or as needed. Per local regulations, LTE and Safety Follow-up Visit pregnancy tests may be performed in clinic.
d Investigator and the Sponsor may re-evaluate a subject's childbearing potential during the study (including the use of FSH values if appropriate)
e If last assessment was completed <11 weeks previously, do not perform at the ET Visit.
f Biomarker samples should be collected prior to study drug administration. Subjects and Investigators will be kept blinded to the results of the CRP test at all visits. Sponsor will be blinded to CRP results in the Main Study only, except the Day 1 Visit. T and B lymphocyte and natural killer (TBNK) results will be blinded to subjects and Investigators at all visits, and will be collected at Day 1 and Week 16. PBMC (North America only) collection on Day 1, Week 4, and Week 16.
[redacted]
j Hepatitis B surface Ag and core Ab, reflex Hepatitis B DNA (as needed), Hepatitis C Ab, reflex Hepatitis C RNA (as needed), HIV 1 and 2 at the Screening Visit.
k Viral monitoring for HBV or HCV, as applicable.
l Imaging performed after enrollment may be done within ±7 days of the scheduled visit.
m Screening MRI to be performed only after a subject has fulfilled criteria for entry to the Main Study. The Week 16 Visit MRI is to be performed only if a Screening MRI is acceptable per central imaging.
n Drug dispensation at Week 2 is for "floater" study drug supply. Please reference your pharmacy manual for instructions on handling floater study drug.
o Self-injection or caregiver training will occur at Day 1 and can be repeated, as needed.

EVENT		Part 2: Long Term Extension												
		Weeks (±3 days)			Weeks (±7 days)							Completion Week 120 (±7 days)	ET (±7 days)	Safety Follow-up (±7 days) [a]
Visit (±window)		18	20	24	28	36	48	60	72	84	96	108			
Patient Reported Outcomes	HAQ-DI: Health Assessment Questionnaire – Disability Index	X	X	X	X	X	X	X	X	X	X	X	X	X	
	FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy – Fatigue Scale						X				X		X	X	
	SF-36v2: 36-item Short-Form Health Survey Version 2						X				X		X	X	
	PsAID-12: 12-item Psoriatic Arthritis Impact of Disease Questionnaire						X				X		X	X	
	CCI [redacted] CCI														
	PGADA: Patient's Global Assessment of Disease Activity	X	X	X	X	X	X	X	X	X	X	X	X	X	
	PGAPI: Patient's Global Assessment of Psoriatic Arthritis Pain Intensity	X	X	X	X	X	X	X	X	X	X	X	X	X	

EVENT		Part 2: Long Term Extension												
		Weeks (±3 days)			Weeks (±7 days)							Completion Week 120 (±7 days)	ET (±7 days)	Safety Follow-up (±7 days) [a]
Visit (±window)		18	20	24	28	36	48	60	72	84	96	108			
Physician Reported Outcomes [a]	PASI including BSA: Psoriasis Area and Severity Index including Body Surface Area		X	X	X	X	X		X		X		X	X	
	mNAPSI: Modified Nail Psoriasis Severity Index		X	X	X	X	X		X		X		X	X	
	PhGAP: Physician's Global Assessment of Psoriasis	X	X	X	X	X	X		X		X		X	X	
	SPARCC Enthesitis Index and LEI: Spondyloarthritis Research Consortium of Canada Enthesitis Index and Leeds Enthesitis Index		X	X	X	X	X		X		X		X	X	
	SJC66 / TJC68: Swollen and Tender Joint Count	X	X	X	X	X	X	X	X	X	X	X	X	X	
	LDI: Leeds Dactylitis Index		X	X	X	X	X		X		X		X	X	
	PhGADA: Physician's Global Assessment of Disease Activity	X	X	X	X	X	X	X	X	X	X	X	X	X	
Safety	Complete Physical Examination						X				X		X	X	
	Symptom-Driven Physical Examination	X	X	X	X	X		X	X	X		X			
	Vital Signs and Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	
	TB Screening and Chest X-ray						X				X			X [b]	
	Pregnancy Test (in clinic)	X	X	X	X	X	X	X	X	X	X	X	X	X	
	Urine Pregnancy Test (at home) [c]	X													X

EVENT		Part 2: Long Term Extension													
		Weeks (±3 days)			Weeks (±7 days)								Completion Week 120 (±7 days)	ET (±7 days)	Safety Follow-up (±7 days) [a]
Visit (±window)		18	20	24	28	36	48	60	72	84	96	108			
Laboratory	Hematology and Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	
	Lipid profile (fasting)						X				X		X	X [b]	
	Serum CRP [d]	X	X	X	X	X	X	X	X	X	X	X	X	X	
	Biomarker Samples [d]						X				X		X		
	Viral Monitoring [e]			X		X	X	X	X	X	X	X	X	X [f]	
	Endocrine: FSH [g]	X													
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X	X		X
Study Drug(s) Dispensation			X	X	X	X	X	X	X	X	X	X			

a Subjects in Europe will have additional Safety Follow-up Visits. These visits will occur 8, 12, and 16 weeks after their last SC injection of study drug and should also be done by phone call unless otherwise required by region. If the subject's last study visit is greater than or equal to 16 weeks from their last SC injection, the additional Safety Follow-up Visits will not be required.

b If last assessment was completed <47 weeks previously, do not perform at the ET Visit.

c For female subjects of childbearing potential only. The site will call the subject every 4 weeks during the LTE or at the Safety Follow-up Visit, if there is not a clinic visit scheduled, in order to obtain results. Per local regulations, at home pregnancy tests may be performed in clinic.

d Biomarker samples should be collected prior to study drug administration. Subjects and Investigators will be kept blinded to the results of the CRP test at all visits. T and B lymphocyte and natural killer (TBNK) results will be blinded to subjects and Investigators at all visits, and will be collected at Week 48, Week 96, and Week 120. PBMC (North America only) collection on Week 48, Week 96, and Week 120.

e Viral monitoring for HBV or HCV, as applicable.

f If last assessment was completed <11 weeks previously, do not perform at the ET Visit.

g Investigator and the Sponsor may re-evaluate a subject's childbearing potential during the study (including the use of FSH values if appropriate).

Appendix 3. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

The administration of filgotinib in embryo-fetal animal development studies resulted in decreased numbers of viable rat fetuses, increased resorptions, and visceral and skeletal malformations. Similar effects were noted in the rabbit. A safety margin relative to human exposure has not been identified. Pregnancy is contraindicated during use of filgotinib.

For participation in this study, all subjects of childbearing potential must agree to the use of *highly effective* contraception as outlined below.

In addition, women of childbearing potential should have a urine pregnancy test every 4 weeks during the study.

1) Definitions

a. Definition of Childbearing Potential

For the purposes of this study, a female born subject is considered of childbearing potential following the initiation of puberty (Tanner stage 2) until becoming post-menopausal, unless permanently sterile or with medically documented ovarian failure.

Women are considered to be in a postmenopausal state when they are ≥54 years of age with cessation of previously occurring menses for ≥12 months without an alternative cause. In addition, women of any age with amenorrhea of ≥12 months may also be considered postmenopausal if their follicle stimulating hormone (FSH) level is in the postmenopausal range (as defined by central laboratory reference ranges) and they are not using hormonal contraception or hormonal replacement therapy.

Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female subject of any age. Bilateral tubal ligation is not considered permanent sterilization. Women who do not meet below criteria for being post-menopausal, are not permanently sterile, or do not have medically documented ovarian failure must have pregnancy testing as outlined by the protocol.

Investigator and the Sponsor may re-evaluate a subject's childbearing potential during the study (including the use of FSH values if appropriate).

b. Definition of Male Fertility

For the purposes of this study, a male born subject is considered fertile after the initiation of puberty unless permanently sterile by bilateral orchidectomy or medical documentation of permanent male infertility. Vasectomy alone is not considered permanent sterilization.

2) Contraception Requirements for Female Subjects

a. Study Drug Effects on Pregnancy and Hormonal Contraception

Filgotinib is contraindicated in pregnancy as there is a possibility of human teratogenicity / fetotoxicity in early pregnancy based on non-clinical data. Data from a drug-drug interaction study of filgotinib and hormonal contraceptives demonstrated that filgotinib does not alter the pharmacokinetics of representative hormonal contraceptives levonorgestrel / ethinyl estradiol. For male subjects, male condom should be used; for their female partners of childbearing potential, an accepted contraceptive method should also be considered. Details are outlined below.

Please refer to the latest version of the filgotinib investigator's brochure for additional information.

b. Contraception for Female Subjects of Childbearing Potential

The inclusion of female subjects of childbearing potential requires the use of highly effective contraceptive measures. Women must have a negative serum pregnancy test at Screening and a negative urine pregnancy test on the Day 1 Visit prior to randomization. Pregnancy tests will be performed at monthly intervals thereafter. In the event of a delayed menstrual period (>one month between menstruations), a pregnancy test must be performed to rule out pregnancy. This is true even for women of childbearing potential with infrequent or irregular periods. Female subjects of childbearing potential must agree to use one of the contraceptive methods below from Screening until either 35 days following the last dose of oral study drug or the contraception duration specified in the local adalimumab (HUMIRA®) label following the last dose of injected study drug (whichever is later).

- Complete abstinence from intercourse of reproductive potential (e.g. heterosexual intercourse). Abstinence is an acceptable method of contraception only when it is in line with the subject's preferred and usual lifestyle.

  Or

- Consistent and correct use of 1 of the following methods of birth control listed below (as approved and available per local standards):

  — Intrauterine device (IUD) with a failure rate of <1% per year

  — Tubal sterilization

  — Essure micro-insert system (provided confirmation of success 3 months after procedure) (Not approved in Japan)

  — Vasectomy in the male partner (provided that the partner is the sole sexual partner and had confirmation of surgical success at least 3 months after procedure, with documentation of sperm-free ejaculate)

These above described methods are considered *preferred methods* of highly effective contraception in this protocol.

Female subjects who wish to use a hormonally based method must agree to use it in conjunction with a barrier method (used either by the female subject or by her male partner). Female subjects who utilize a hormonal contraceptive as one of their birth control methods must have consistently used the same method for at least three months prior to study dosing. Hormonally-based contraceptives and barrier methods permitted for use in this protocol are as follows:

- Hormonal methods (subject must agree to use with a barrier method, preferably, with a male condom)
  - Oral contraceptives (either combined estrogen / progestin or progesterone only)
  - Injectable progesterone (Not approved in Japan)
  - Subdermal Implants of levonorgestrel (Not approved in Japan)
  - Transdermal contraceptive patch (Not approved in Japan)
  - Contraceptive vaginal ring
- Barrier methods (subject must agree to use with a hormonal method)
  - Male or female condom (with or without spermicide)
  - Diaphragm with spermicide (Not approved in Japan)
  - Cervical cap with spermicide (Not approved in Japan)
  - Sponge with spermicide (Not approved in Japan)

All female subjects must also agree to refrain from egg donation and in vitro fertilization during study participation and until either 35 days following the last dose of oral study drug or the contraception duration specified in the local adalimumab (HUMIRA®) label following the last dose of injected study drug (whichever is later).

3) Contraception Requirements for Male Subjects

It is theoretically possible that a relevant systemic concentration may be achieved in a female partner from exposure to the male subject's seminal fluid. Therefore, male subjects with female partners of childbearing potential must agree to use condoms during study participation and for 90 days after the last study drug dose. Female partners of male study subjects should consider using one of the above methods of contraception as well. Male subjects must also agree to refrain from sperm donation during treatment and until at least 90 days after the end of dosing.

4) Unacceptable Birth Control Methods

Birth control methods that are unacceptable include periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM). Female condom and male condom should not be used together.

5) Procedures to be Followed in the Event of Pregnancy

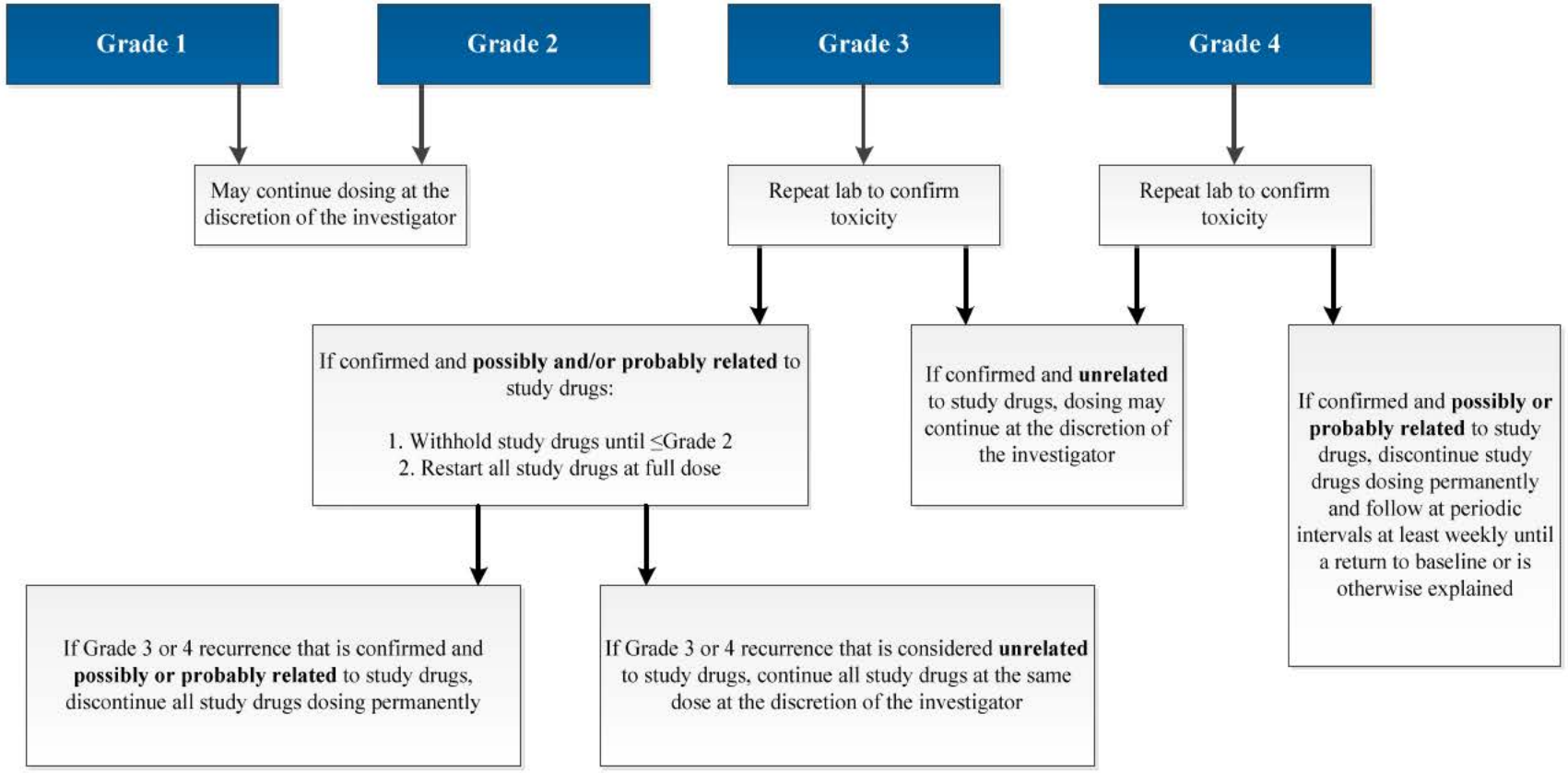
Subjects will be instructed to notify the investigator if they become pregnant at any time during the study, or if they become pregnant within 35 days of last study drug dose. Subjects who become pregnant or who suspect that they are pregnant during the study must report the information to the investigator and discontinue all the study drugs immediately. These subjects will be asked to continue in the study without taking study drug through the completion of the main study. Male subjects whose partner has become pregnant or suspects she is pregnant during the study or up to 90 days after the last dose of study drug are to report the information to the investigator.

Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.7.2.1.

6) Pregnancy Testing

All females of childbearing potential will have urine pregnancy testing every 4 weeks during the dosing period through the Safety Follow-up Visit (28-35 days after their last dose of study drug). During the periods where study visits are every 6-8 weeks, women should continue to have pregnancy tests every 4 weeks, using home pregnancy urine tests that will be provided to them. The site will call the subject every 4 weeks to obtain results of these pregnancy tests and will record the information in the source documents and eCRF. If a positive urine pregnancy test is reported, the subject will be asked to return to the clinic for a confirmatory serum pregnancy test.

Appendix 4. Management of Clinical and Laboratory Adverse Events



For study specific interruption and stopping criteria, please refer to Section 3.5.

Appendix 5. Laboratory Assessment Table

Hematology	Chemistry	Urinalysis	Other
Hematocrit Hemoglobin Platelet count Red blood cell (RBC) count Red blood cell indices: RBC Morphology and MCV MCH MCHC White blood cell (WBC) count Differentials (absolute and percentage), including: Lymphocytes Monocytes Neutrophils Eosinophils Basophils	Alkaline phosphatase Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Gamma-glutamyl transpeptidase (GGT) Total bilirubin Direct and indirect bilirubin Total protein Albumin Bicarbonate Blood urea nitrogen (BUN) Calcium Chloride Serum creatinine* Glucose Phosphorus Magnesium Potassium Sodium Amylase Lipase <u>Lipid profile (fasting)</u>: Triglycerides Cholesterol and its subfractions (high-density lipoprotein [HDL] and low-density lipoprotein [LDL])	Appearance Blood Color Glucose Specific gravity Nitrites Leukocyte esterase pH Protein Urobilinogen Reflex to microscopic urinalysis if dipstick result is abnormal.	Urine drug screen Leukocyte subsets (TBNK blinded to subjects and investigators) vfPBMC** C-reactive protein (hsCRP) (blinded to subjects and investigators for all visits, blinded to Sponsor for all Main Study visits except Day 1 Visit) CCI QuantiFERON®- TB GOLD Plus††
Endocrine at screening only		**Serology**	**Pregnancy**
Hemoglobin A1c TSH FSH (for women only)†††		Hepatitis BsAg and core Ab (if positive core Ab, then reflex Hep B DNA) Hepatitis C Ab (if positive, then reflex HCV RNA) HIV	*In females of childbearing potential:* Serum β-hCG (Screening and if positive urine β-hCG) Urine β-hCG (all other visits)†

* Creatinine clearance is calculated by the Cockcroft-Gault equation {Cockcroft 1976} using actual body weight (BW).

Male: CL_{cr} (mL / min) = $\frac{[140 - \text{age (years)}] \times \text{BW(kg)}}{72 \times [\text{Serum Creatinine } (\text{in} \frac{\text{mg}}{\text{dL}})]}$

Female: CL_{cr} (mL / min) = $\frac{[140 - \text{age (years)}] \times \text{BW(kg)} \times 0.85}{72 \times [\text{Serum Creatinine } (\text{in} \frac{\text{mg}}{\text{dL}})]}$

** vfPBMCs collected in North America only.

† During the periods where study visits are every 6-8 weeks, women should continue to have pregnancy tests every 4 weeks, using home pregnancy urine tests that will be provided to them. The site will call the subject every 4 weeks to obtain results of these pregnancy tests and will record the information in the source documents and eCRF.

†† In the event QuantiFERON®-TB GOLD Plus is not available, an equivalent TB test may be substituted by the central lab.

††† Investigator and the Sponsor may re-evaluate a subject's childbearing potential during the study (including the use of FSH values if appropriate).

Appendix 6. Primary and Key Secondary Null Hypotheses

The primary null hypotheses to be tested are:

H1: Filgotinib 200 mg is not different to placebo based on the response rate of ACR20 at Week 12

H2: Filgotinib 100 mg is not different to placebo based on the response rate of ACR20 at Week 12

Hypotheses on the key secondary endpoints will only be tested if the primary hypothesis H1 or H2 on that dosing regimen is rejected. The following list is the full list of all the null hypotheses on the key secondary endpoints to be tested. The order of the key secondary null hypotheses to be tested will be specified in the SAP and is not reflected below.

H3: Filgotinib 200 mg is not different to placebo based on the response rate of ACR50 at Week 12

H4: Filgotinib 100 mg is not different to placebo based on the response rate of ACR50 at Week 12

H5: Filgotinib 200 mg is not different to placebo based on the change from Baseline in HAQ-DI at Week 12

H6: Filgotinib 100 mg is not different to placebo based on the change from Baseline in HAQ-DI at Week 12

H7: Filgotinib 200 mg is not different to placebo based on the change from Baseline in SF-36v2 PCS at Week 16

H8: Filgotinib 100 mg is not different to placebo based on the change from Baseline in SF-36v2 PCS at Week 16

H9: Filgotinib 200 mg is not different to placebo based on the change from Baseline in LEI at Week 16, in subjects with enthesitis at Baseline

H10: Filgotinib 100 mg is not different to placebo based on the change from Baseline in LEI at Week 16, in subjects with enthesitis at Baseline

H11: Filgotinib 200 mg is not different to placebo based on the response rate of PASI75 at Week 16, in subjects with psoriasis covering ≥3% of the BSA at Baseline

H12: Filgotinib 100 mg is not different to placebo based on the response rate of PASI75 at Week 16, in subjects with psoriasis covering ≥3% of the BSA at Baseline

H13: Filgotinib 200 mg is not different to placebo based on the response rate of MDA at Week 16

H14: Filgotinib 100 mg is not different to placebo based on the response rate of MDA at Week 16

H15: Filgotinib 200 mg preserves no more than 50% of the effect of adalimumab (as compared to placebo) on the response rate of ACR20 at Week 12

H16: Filgotinib 100 mg preserves no more than 50% of the effect of adalimumab (as compared to placebo) on the response rate of ACR20 at Week 12

H17: Filgotinib 200 mg is not different to placebo based on the change from Baseline in FACIT-Fatigue at Week 16

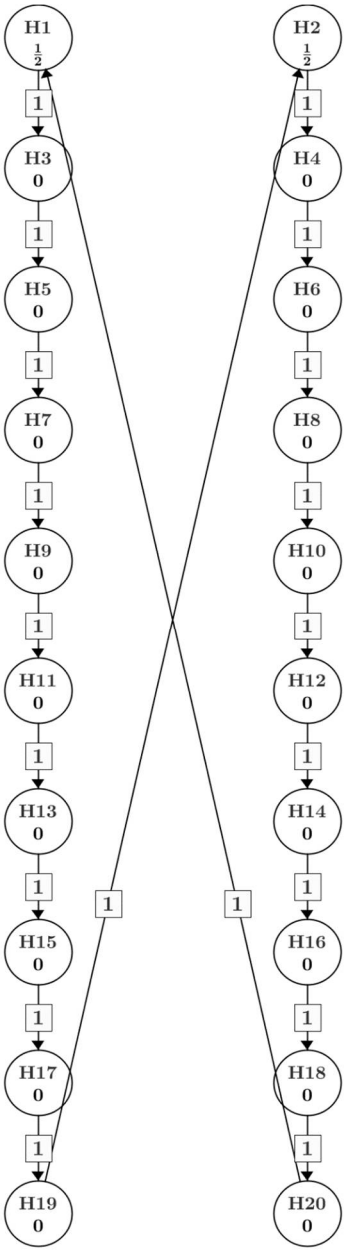
H18: Filgotinib 100 mg is not different to placebo based on the change from Baseline in FACIT-Fatigue at Week 16

H19: Filgotinib 200 mg is not different to placebo based on the change from Baseline in LDI at Week 16, in subjects with dactylitis at Baseline

H20: Filgotinib 100 mg is not different to placebo based on the change from Baseline in LDI at Week 16, in subjects with dactylitis at Baseline

Appendix 7. Hypothesis Testing Strategy

Note: Below figure is for illustration purpose and does not reflect the order of key secondary hypotheses.



Appendix 8. Protocol, Day Numbering

Protocol Day Numbering			# Calendar Days after Day 1	Example Visit Date
Start of 1st Week	Monday	Day 1	-	16-Sep-19
	Tuesday	Day 2	1	17- Sep-19
	Wednesday	Day 3	2	18- Sep-19
	Thursday	Day 4	3	19- Sep-19
	Friday	Day 5	4	20-Sep-19
	Saturday	Day 6	5	21-Sep-19
	Sunday	Day 7	6	22-Sep-19
Start of 2nd Week	Monday	Day 8	7	23-Sep-19
	Tuesday	Day 9	8	24-Sep-19
	Wednesday	Day 10	9	25-Sep-19
	Thursday	Day 11	10	26-Sep-19
	Friday	Day 12	11	27-Sep-19
	Saturday	Day 13	12	28-Sep-19
	Sunday	Day 14	13	29-Sep-19
Start of 3rd Week	Monday	Day 15	14	30-Sep-19
	Tuesday	Day 16	15	1-Oct-19
	Wednesday	Day 17	16	2-Oct-19
	Thursday	Day 18	17	3-Oct-19
	Friday	Day 19	18	4-Oct-19
	Saturday	Day 20	19	5-Oct-19
	Sunday	Day 21	20	6-Oct-19

NOTE: Vendors may have different ***Day Numbering*** (i.e. start with Day 0); however, the ***# Calendar Days after Day 1*** will remain consistent.

Appendix 9. HAQ-DI: Health Assessment Questionnaire – Disability Index

HEALTH ASSESSMENT QUESTIONNAIRE

PATKEY#_____
QUESTDAT_____
_

Name_____ **Date**_____

In this section we are interested in learning how your illness affects your ability to function in daily life. Please feel free to add any comments on the back of this page.

HAQADMIN_____

Please check the response which best describes your usual abilities OVER THE PAST WEEK:

QUESTYPE_____

PMSVIS_____
RASTUDY_____

	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To Do
DRESSING & GROOMING				
Are you able to:				
- Dress yourself, including tying shoelaces and doing buttons?	____	____	____	____
- Shampoo your hair?	____	____	____	____
ARISING				
Are you able to:				
- Stand up from a straight chair?	____	____	____	____
- Get in and out of bed?	____	____	____	____
EATING				
Are you able to:				
- Cut your meat?	____	____	____	____
- Lift a full cup or glass to your mouth?	____	____	____	____
- Open a new milk carton?	____	____	____	____
WALKING				
Are you able to:				
- Walk outdoors on flat ground?	____	____	____	____
- Climb up five steps?	____	____	____	____

QUESTNUM_____
DRESSNEW_____
RISENEW_____
EATNEW_____
WALKNEW_____

Please check any AIDS OR DEVICES that you usually use for any of these activities:

_____ Cane
_____ Walker
_____ Crutches
_____ Wheelchair
_____ Devices used for dressing (button hook, zipper pull, long-handled shoe horn, etc.)
_____ Built up or special utensils
_____ Special or built up chair
_____ Other (Specify:_____)

DRSGASST_____
RISEASST_____
EATASST_____
WALKASST_____

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

_____ Dressing and Grooming
_____ Arising
_____ Eating
_____ Walking

1

Please check the response which best describes your usual abilities OVER THE PAST WEEK:

	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To Do	
HYGIENE					
Are you able to:					
- Wash and dry your body?	____	____	____	____	
- Take a tub bath?	____	____	____	____	
- Get on and off the toilet?	____	____	____	____	HYGNNEW_____
REACH					
Are you able to:					
- Reach and get down a 5 pound object (such as a bag of sugar) from just above your head?	____	____	____	____	
- Bend down to pick up clothing from the floor?	____	____	____	____	REACHNEW_____
GRIP					
Are you able to:					
- Open car doors?	____	____	____	____	
- Open jars which have been previously opened?	____	____	____	____	
- Turn faucets on and off?	____	____	____	____	GRIPNEW_____
ACTIVITIES					
Are you able to:					
- Run errands and shop?	____	____	____	____	
- Get in and out of a car?	____	____	____	____	
- Do chores such as vacuuming or yardwork?	____	____	____	____	ACTIVNEW_____

Please check any AIDS OR DEVICES that you usually use for any of these activities:

____ Raised toilet seat
____ Bathtub seat
____ Jar opener (for jars previously opened)
____ Bathtub bar
____ Long-handled appliances for reach
____ Long-handled appliances in bathroom
____ Other (Specify: _____)

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

____ Hygiene
____ Reach
____ Gripping and opening things
____ Errands and chores

HYGNASST_____
RCHASST_____
GRIPASST_____
ACTVASST_____

We are also interested in learning whether or not you are affected by pain because of your illness.

How much pain have you had because of your illness IN THE PAST WEEK:

PLACE A VERTICAL (I) MARK ON THE LINE TO INDICATE THE SEVERITY OF THE PAIN.

NO PAIN 0 _____ SEVERE PAIN 100

PAINSCAL_____

Appendix 10. FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy -Fatigue Scale

FACIT Fatigue Scale (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please select one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

English (Universal)

16 November 2007

Appendix 11. SF-36v2: 36-Item Short-Form Health Survey Version 2

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.
Thank you for completing this survey!

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. **In general, would you say your health is:**

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. **<u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?**

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g Walking more than a mile	☐ 1	☐ 2	☐ 3
h Walking several hundred yards	☐ 1	☐ 2	☐ 3
i Walking one hundred yards	☐ 1	☐ 2	☐ 3
j Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

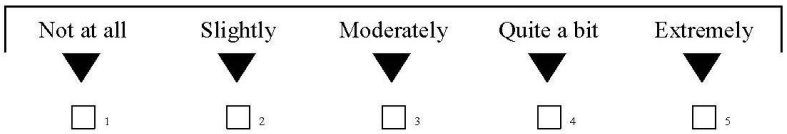
4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

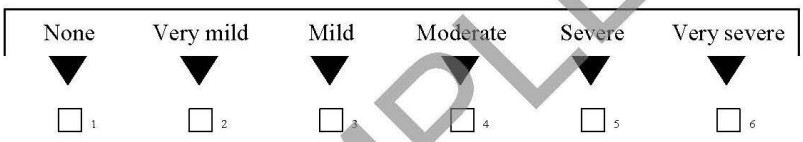
5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

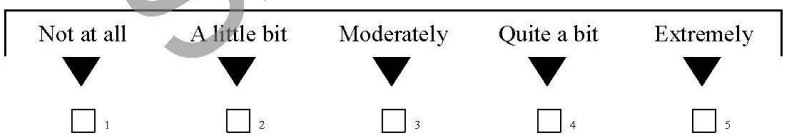
6. **During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?**



7. **How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?**



8. **During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?**



9. These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past 4 weeks</u>…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

Appendix 12. PsAID-12: 12-item Psoriatic Arthritis Impact of Disease Questionnaire

The EULAR Psoriatic Arthritis Impact of Disease: PsAID12 for clinical practice

We want you to indicate how much your psoriatic arthritis impacts your health.
Please tell us how you have been feeling this last week.

1. Pain

Circle the number that best describes the pain you felt due to your psoriatic arthritis during the last week:

None	0	1	2	3	4	5	6	7	8	9	10	Extreme

For office use only
Result x3 ☐

2. Fatigue

Circle the number that best describes the overall level of fatigue due to your psoriatic arthritis you have experienced during the last week:

No fatigue	0	1	2	3	4	5	6	7	8	9	10	Totally exhausted

Result x2 ☐

3. Skin problems

Circle the number that best describes the skin problems including itching you felt due to your psoriatic arthritis during the last week:

None	0	1	2	3	4	5	6	7	8	9	10	Extreme

Result x2 ☐

4. Work and/or leisure activities

Circle the number that best describes the difficulties you had to participate fully in work and/or leisure activities due to your psoriatic arthritis during the last week:

None	0	1	2	3	4	5	6	7	8	9	10	Extreme

Result x2 ☐

5. Functional capacity

Circle the number that best describes the difficulty you had in doing daily physical activities due to your psoriatic arthritis during the last week:

No difficulty	0	1	2	3	4	5	6	7	8	9	10	Extreme difficulty

Result x2 ☐

6. Discomfort

Circle the number that best describes the feeling of discomfort and annoyance with everyday tasks due to your psoriatic arthritis during the last week:

None	0	1	2	3	4	5	6	7	8	9	10	Extreme

Result x2 ☐

7. Sleep disturbance

Circle the number that best describes the sleep difficulties (i.e., resting at night) you felt due to your psoriatic arthritis during the last week:

No difficulty	0	1	2	3	4	5	6	7	8	9	10	Extreme difficulty

Result x2 ☐

1

8. Coping

Considering your psoriatic arthritis overall, how well did you cope (manage, deal, make do) with your psoriatic arthritis during the last week?

Very well	0	1	2	3	4	5	6	7	8	9	10	Very poorly

For office use only
Result x1 ☐

9. Anxiety, fear and uncertainty

Circle the number that best describes the level of anxiety, fear and uncertainty (for example about the future, treatments, fear of loneliness) due to your psoriatic arthritis you have experienced during the last week:

None	0	1	2	3	4	5	6	7	8	9	10	Extreme

Result x1 ☐

10. Embarrassment and/or shame

Considering your psoriatic arthritis overall, circle the number that best describes the level of embarrassment and/or shame due to your appearance experienced during the last week:

None	0	1	2	3	4	5	6	7	8	9	10	Extreme

Result x1 ☐

11. Social participation

Circle the number that best describes the difficulties you had to participate fully in social activities (including relationships with family and/or people very close to you) due to your psoriatic arthritis during the last week:

None	0	1	2	3	4	5	6	7	8	9	10	Extreme

Result x1 ☐

12. Depression

Circle the number that best describes the level of depression due to your psoriatic arthritis you have experienced during the last week:

None	0	1	2	3	4	5	6	7	8	9	10	Extreme

Result x1 ☐

THANK YOU FOR ANSWERING THIS QUESTIONNAIRE

Final PsAID out of 20

Add up the ☐ and divide by 10: ☐

PsAID12 SCORING AND CALCULATION RULES

The PsAID is calculated based on 12 Numerical rating scales (NRS) questions. Each NRS is assessed as a number between 0 and 10.

Calculation

PsAID final value =
(PsAID1 (pain) NRS value (range 0-10) x 3)
+ (PsAID2 (fatigue) NRS value (range 0-10) x 2)
+ (PsAID3 (skin) NRS value (range 0-10) x 2)
+ (PsAID4 (Work and/or leisure activities) NRS value (range 0-10) x 2)
+ (PsAID5 (function) NRS value (range 0-10) x 2)
+ (PsAID6 (discomfort) NRS value (range 0-10) x 2)
+ (PsAID7 (sleep) NRS value (range 0-10) x 2)
+ (PsAID8 (coping) NRS value (range 0-10) x 1)
+ (PsAID9 (anxiety) NRS value (range 0-10) x 1)
+ (PsAID10 (embarrassment) NRS value (range 0-10) x 1)
+ (PsAID11 (social life) NRS value (range 0-10) x 1)
+ (PsAID12 (depression) NRS value (range 0-10) x 1)

The total is divided by 20.

Thus, the range of the final PsAID value is 0-10 where higher figures indicate worse status.

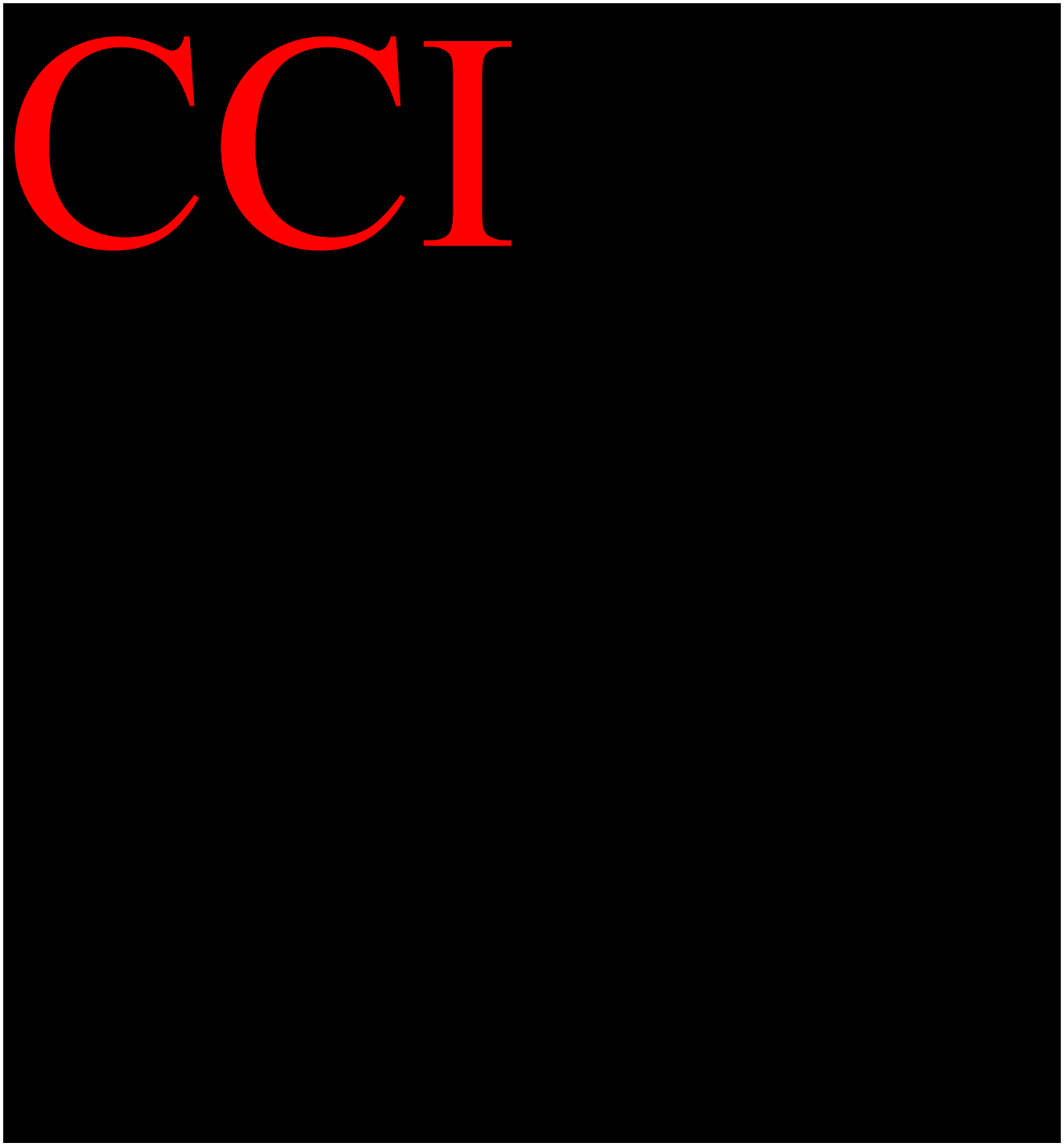
Missing data imputation

If one of the 12 NRS values composing the PsAID is missing, the imputation is as follows:
calculate the mean value of the 11 other (non-missing) NRS (range, 0-10)
impute this value for the missing NRS
Then, calculate the PsAID as explained above.

If 2 or more of the NRS are missing, the PsAID is considered as missing value (no imputation).

3


CCI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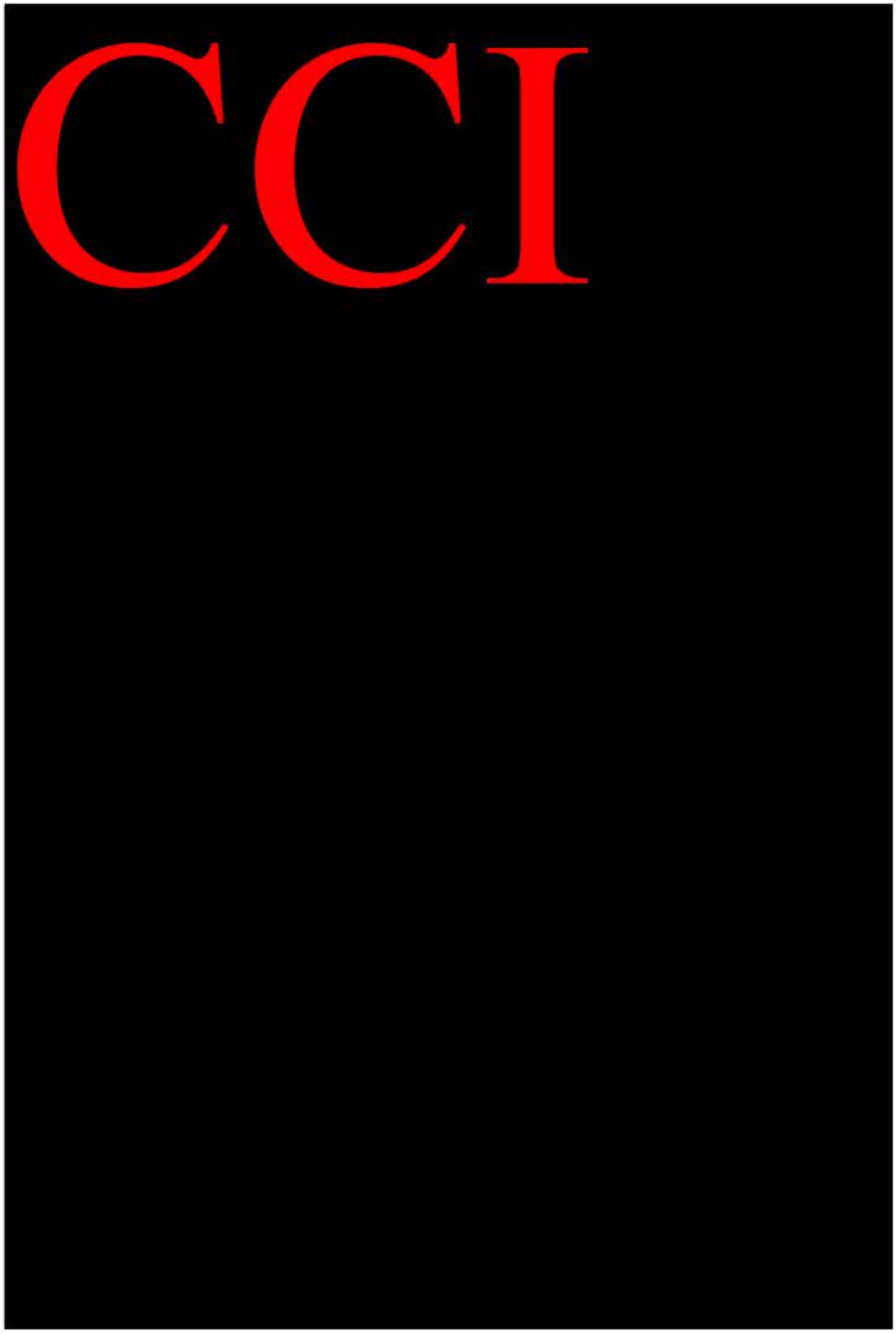
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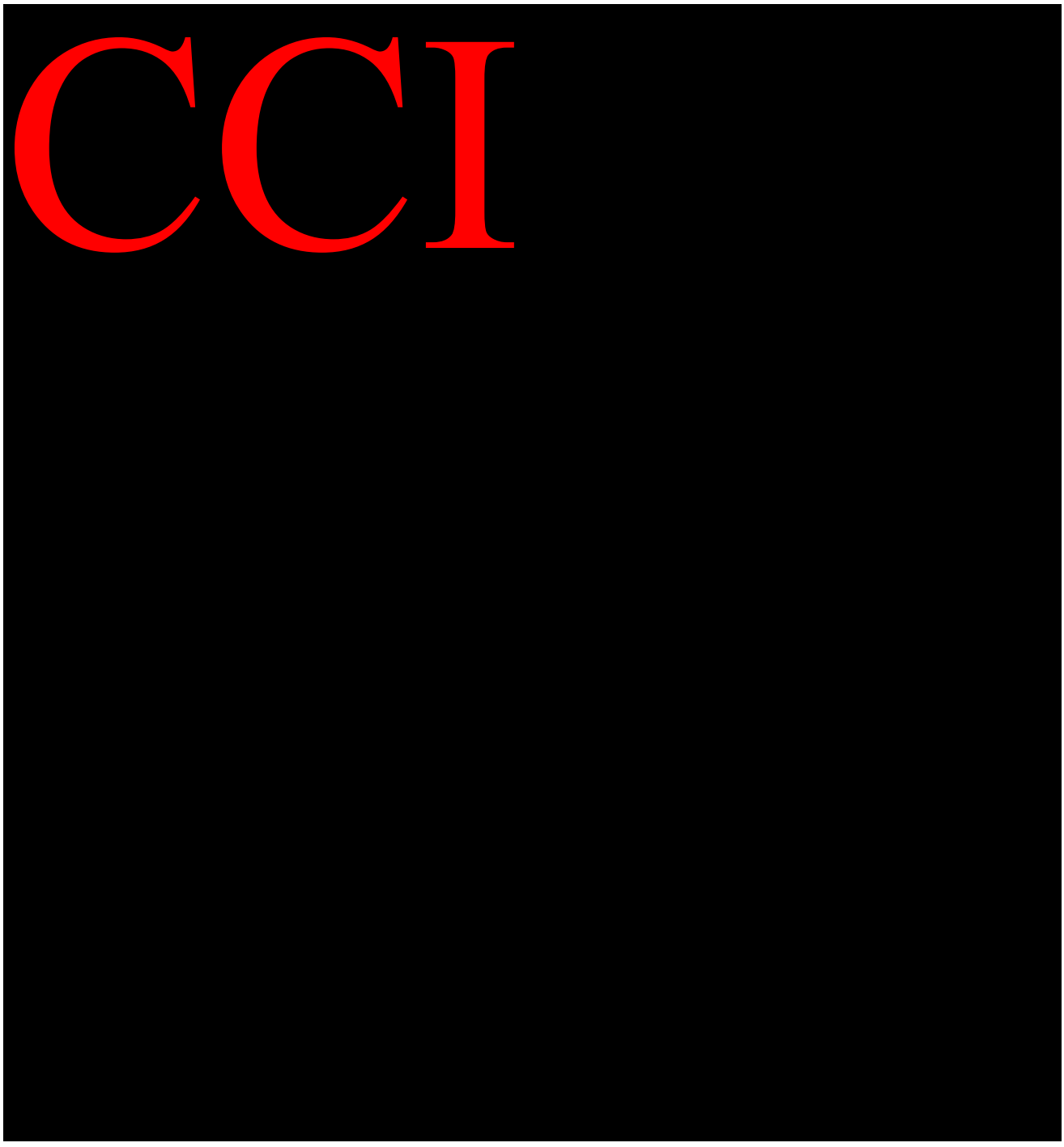
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Appendix 17. PGADA: Patient's Global Assessment of Disease Activity

Patient's Global Assessment of Disease Activity

Instructions:

Considering all the ways psoriatic arthritis affects you, please indicate with a vertical mark (|) through the horizontal line how well you are doing today?

0 100

Very Well Very Poor

Note: The VAS scale must be 100 mm long.

Appendix 18. PGAPI: Patient's Global Assessment of Psoriatic Arthritis Pain Intensity

Patient's Assessment of PsA Pain Intensity

Instructions:

Please indicate with a vertical mark (|) through the horizontal line the most pain you had from your psoriatic arthritis today.

0 100

No pain Unbearable pain

Note: the VAS scale must be 100 mm long.

Appendix 19. CASPAR: Classification Criteria for Psoriatic Arthritis

CASPAR Classification Criteria for Psoriatic Arthritis

The classification of PsA based on the CASPAR criteria requires the presence of established inflammatory arthritis (joints, spine, or enthuses) with at least 3 points from the following 5 features:

- Current psoriasis, OR

  A history of psoriasis, OR

  A family history of psoriasis
- Current or prior history of dactylitis
- Radiographic evidence of juxta-articular new-bone formation
- Absence of serum rheumatoid factor
- Nail dystrophy

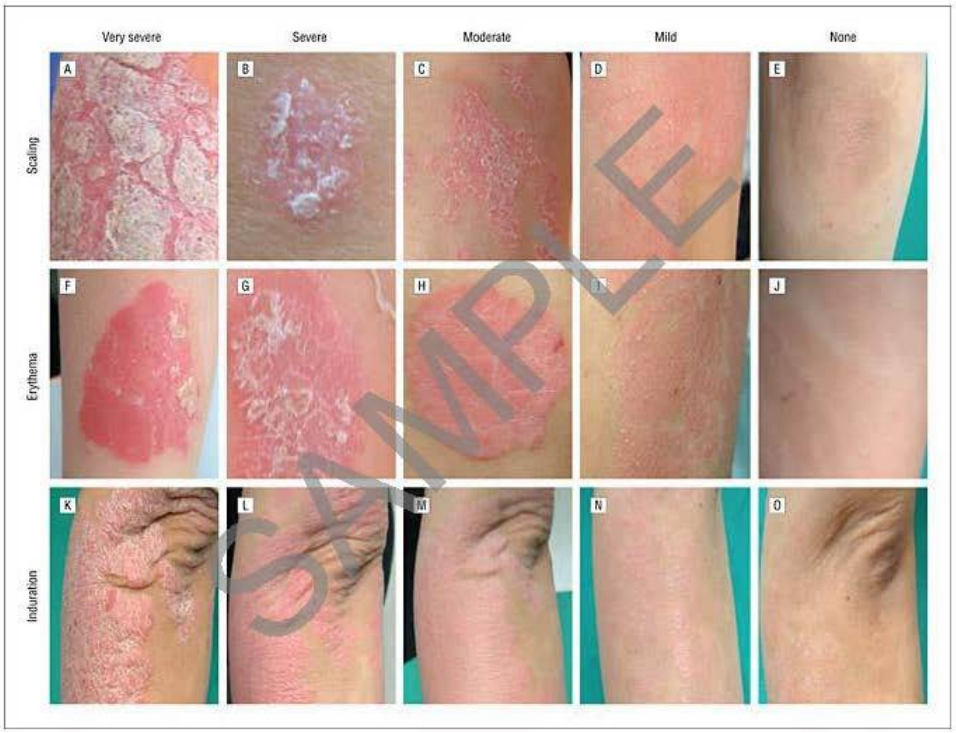
Current psoriasis is assigned 2 points, while all other clinical features are assigned 1 point.

Appendix 20. PASI including BSA: Psoriasis Area and Severity Index including Body Surface Area

Psoriasis Area and Severity Index (PASI), Including Body Surface Area (BSA)

Intensity

A representative area of psoriasis is selected for each body region (head and neck, upper limbs, trunk, lower limbs). The intensity of erythema, induration and scaling of the psoriasis is assessed as none (0), mild (1), moderate (2), severe (3) or very severe (4).



Body surface area

The percentage area affected by psoriasis is evaluated in the 4 regions of the body. In each region, the area is expressed as nil 0 (0), >0 - <10% (1), 10 - <30% (2), 30 - <50% (3), 50 - <70% (4), 70 - <90% (5) or 90 - 100% (6)

Appendix 21. mNAPSI: Modified Nail Psoriasis Severity Index

Modified Nail Psoriasis Severity Index (mNAPSI)

mNAPSI will be collected only in subjects with psoriatic nail involvement. This tool will ask you to assess each nail abnormality for each of a subject's nails. If you question which grade to give, your answer should be the lower of the grades. Three features or groups of features (pitting, onycholysis together with oil-drop dyschromia, and crumbling) of each fingernail will be graded on a scale from zero to 3, according to the directions below. Four features (leukonychia, splinter hemorrhages, hyperkeratosis, and red spots in the lunula) will be graded as either present or absent for each fingernail.

1. Onycholysis: Separation of the nail plate from the nail bed. The separated part of the nail is opaque and can have white, yellow, or greenish tinge. If there is a piece of nail missing, estimate where the nail normally would have ended at the end of the nail bed, and count that missing part as involved in onycholysis.

Oil-drop (salmon patch) dyschromia: Reddish-brown discoloration under the nail plate.

Onycholysis and oil-drop dyschromia are considered together. When looking at the nail, combine the total percentage area of the nail that is affected by either and use that combined total to score the nail.

Score: Percent of nail with onycholysis or oil-drop dyschromia present

- 0 No onycholysis or oil drop dyschromia present
- 1 1–10% of the nail has onycholysis or oil-drop dyschromia
- 2 11–30% of the nail has onycholysis or oil-drop dyschromia
- 3 >30% of the nail has onycholysis or oil-drop dyschromia

2. Pitting: Small, sharply defined depressions in the nail surface. Pits are discrete abnormalities ("icepick-like"). If there is nail plate crumbling that is confluent with pits, do not score for pits. If the pits are separate from crumbling, they may be scored regardless of whether crumbling is present or not.

Score: Number of pits

- 0 0
- 1 1–10
- 2 11–49
- 3 ≥ 50

3. Nail plate crumbling: Crumbling or fragmentation of friable nail plate which may be associated with confluent pitting. Crumbling involves alteration of the nail plate surface. Horizontal ridging of the nail, "wave-like" appearance, and horizontal lines are all features of crumbling.

Score: Percent of nail with crumbling present

- 0 No crumbling
- 1 1–25% of the nail has crumbling
- 2 26–50% of the nail has crumbling
- 3 > 50% of the nail has crumbling

The next 4 abnormalities are scored only by their presence or absence. A score of 1 indicates present and a score of zero indicates not present

1. Leukonychia: White spots in the nail plate due to psoriasis in the mid matrix. Leukonychia are just color changes. If it appears that there is depression or irregularity to the nail surface, this may be pitting or crumbling, not leukonychia. If the leukonychia is adjacent to, or confluent with crumbling or pits, it is counted as part of the crumbling or pitting and not as a separate abnormality.

2. Splinter hemorrhages: Small, longitudinal, linear, dark brown hemorrhage under the fingernail.

3. Nail bed hyperkeratosis: Thickened keratin in the nail bed.

4. Red spots in the lunula: Small pink or red macules in the lunula.

Source: Casell SE et al [22]

Appendix 22. PhGAP: Physician's Global Assessment of Psoriasis

Physician's Global Assessment of Psoriasis

The physician will give a score on the patient's psoriasis disease activity, according to the following grades:

Induration (I) (averaged over all lesions; use the National Psoriasis Foundation Reference card for measurement)

- 0 = no evidence of plaque elevation
- 1 = minimal plaque elevation, = 0.25 mm
- 2 = mild plaque elevation, = 0.5 mm
- 3 = moderate plaque elevation, = 0.75 mm
- 4 = marked plaque elevation, = 1 mm
- 5 = severe plaque elevation, = 1.25 mm or more

Erythema (E) (averaged over all lesions)

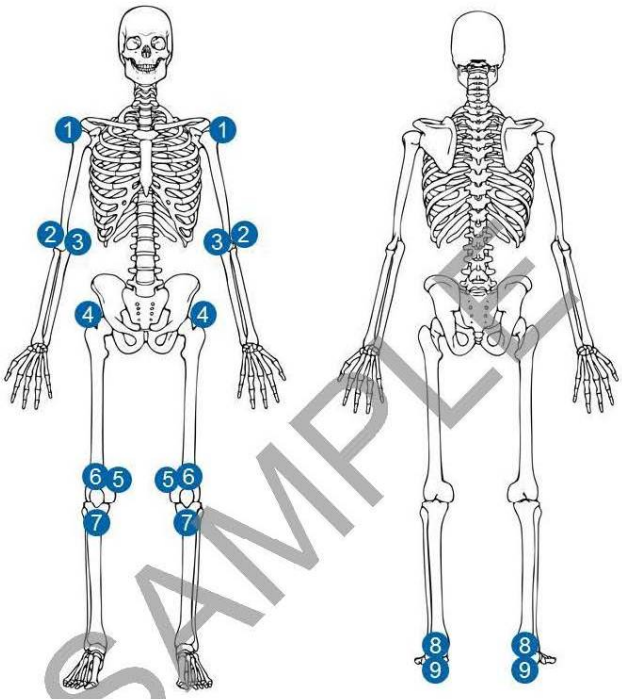
- 0 = no evidence of erythema, hyperpigmentation may be present
- 1 = faint erythema
- 2 = light red coloration
- 3 = moderate red coloration
- 4 = bright red coloration
- 5 = dusky to deep red coloration

Scaling (S) (averaged over all lesions)

- 0 = no evidence of scaling
- 1 = minimal; occasional fine scale over less than 5% of the lesion
- 2 = mild; fine scale dominates
- 3 = moderate; coarse scale predominates
- 4 = marked; thick nontenacious scale dominates
- 5 = severe; very thick tenacious scale predominates

Appendix 23. SPARCC Enthesitis Index and LEI: Spondyloarthritis Research Consortium of Canada Enthesitis Index and Leeds Enthesitis Index

The following will be assessed within the electronic Clinical Outcomes Assessment for enthesitis:



1. Supraspinatus insertion (SPARCC Only)
2. Lateral epicondyle humerus (Both SPARCC and LEI)
3. Medial epicondyle humerus (SPARCC Only)
4. Greater trochanter (SPARCC Only)
5. Medical condyle femur (LEI Only)
6. Quadriceps insertion into the superior border of patella (SPARCC Only)
7. Patellar tendon insertion into the inferior pole of patella OR tibia tuberosity (SPARCC Only)
8. Achilles tendon (Both SPARCC and LEI)
9. Insertion plantar fascia (SPARCC Only)

Appendix 24. SJC66 / TJC68: Swollen and Tender Joint Count

An overview of the (66 / 68) joints to be assessed bilaterally are provided below:

- Temporomandibular
- Sternoclavicular
- Acromioclavicular
- Shoulder
- Elbow
- Wrist
- Metacarpophalangeal: first, second, third, fourth, fifth
- Proximal interphalangeal: first, second, third, fourth, fifth
- Distal interphalangeal: second, third, fourth, fifth
- Hip [1]
- Knee
- Ankle
- Tarsus
- Metatarsophalangeal: first, second, third, fourth, fifth
- Proximal interphalangeal (toe) : first, second, third, fourth, fifth

Replaced / missing (or otherwise not assessable) joints should be documented at Day 1 and omitted from further evaluation during the study.

[1] Assessed for tenderness only

Appendix 25. LDI: Leeds Dactylitis Index

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The Leeds Dactylometer

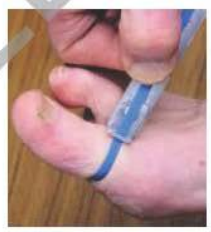
Dactylitis has been defined as "*uniform swelling such that the soft tissues between the metacarpophalangeal and proximal interphalangeal, proximal and distal interphalangeal, and/or distal interphalangeal joint and digital tuft are diffusely swollen to the extent that the actual joint swelling could no longer be independently recognised.*"(1) Dactylitis is a hallmark clinical feature in patients with spondyloarthropathies (SpA) and is commonly observed in psoriatic arthritis.

Dactylitis occurs in 16-48% of cases of psoriatic arthritis (PsA). Acute dactylitis has been shown to be a clinical indicator of disease severity in PsA; conversely, chronic, non-tender diffuse dactylitic swelling may be less clinically significant (2). Dactylitis is due to inflammation in the majority of tissues in the digit - the tendon sheaths, joints, bones and soft-tissues in between (3). Recurrent dactylitis, often in the same digit(s), may be the only clinical manifestation of PsA.

The only validated tool for assessing dactylitis is the Leeds Dactylometer (4). The validity of this instrument has been assessed using the OMERACT filter. The instrument and tool have demonstrated good evidence of responsiveness in a clinical trial (5). In addition, the instrument incorporates a definition of dactylitis (a 10% difference in the ratio of circumference of the affected digit to the contralateral digit). Using the contralateral digit as a normator enables any inter-individual variation in measurement technique to be minimised. The instrument comes with an assessment sheet (see reverse) which provides automatic computation of the Leeds Dactylitis Index.

How to use the Leeds Dactylometer

1. The fingers and toes are visually inspected by the examiner. Those digits which look dactylitic are measured.
2. Slip the loop of the Dactylometer around the base of the digit adjacent to the web space. Pull the indicator strip tight so that the base of the digit blanches slightly (see illustration). The collar of the device should be firmly pressed against the base of the digit, as illustrated.
3. Record the circumference in mm on the Dactylometer record sheet
4. Repeat the procedure on the contralateral digit
5. If both ipsilateral and contralateral digits are thought to be dactylitic then use the reference range (given at the foot of the sheet) as the comparator.
6. Only record the digits with a 10% difference in circumference
7. Squeeze the digit *between* the joints and record the tenderness as indicated
8. Calculate the total score as indicated or enter the values in the Excel spreadsheet.



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(1) Rothschild BM, Pingitore C, Eaton M. Dactylitis: implications for clinical practice. Seminars in Arthritis & Rheumatism 1998; 28(1):41-47.

(2) Brockbank JE, Stein M, Schentag CT, Gladman DD. Dactylitis in psoriatic arthritis: a marker for disease severity? Ann Rheum Dis 2005; 64(2):188-190.

(3) Healy PJ, Groves C, Chandramohan M, Helliwell PS. MRI changes in psoriatic dactylitis extent of pathology, relationship to tenderness and correlation with clinical indices. Rheumatology 2008; 47(1):92-95.

(4) Helliwell PS, Firth J, Ibrahim GH, Melsom RD, Shah I, Turner DE. Development of an assessment tool for dactylitis in patients with psoriatic arthritis. Journal of Rheumatology 32(9):1745-50, 2005.

(5) Healy PJ, Helliwell PS. Measuring dactylitis in clinical trials: which is the best instrument to use? [see comment]. Journal of Rheumatology 34(6):1302-6, 2007.

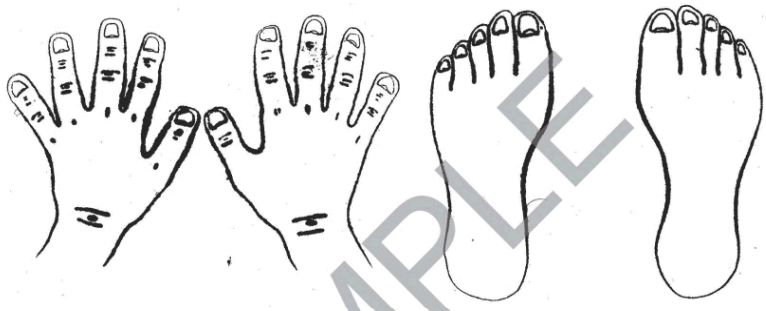
DACTYLITIS SCORE SHEET

Doc 164-1 28th June 2010

Address Label

Date:

Please indicate dactylitic joints



Finger / Toe	Circumference Involved Digit (A)	Contralateral Digit (or Tables) (B)	Tenderness Score (C)	Final Score: [{(A/B)-1}x100]xC
TOTAL				

Standard reference: Table - hands

Digit	Men	Women
Thumb	70	58
Index	63	54
Middle	63	54
Ring	59	50
Little	52	44

Table – feet

Digit	Men	Women
Great toe	82	72
Second	52	46
Middle	50	44
Fourth	50	44
Little	52	45

Tenderness score: response to squeeze
0 no tenderness
1 tender
2 tender and wince
3 tender and withdraw

Appendix 26. PhGADA: Physician's Global Assessment of Disease Activity

Physician's global assessment of disease activity

Place a mark on the line below to indicate PsA disease activity (independent of the subject's self-assessment):